COMMENTARY

The 7th Canadian Symposium on Hepatitis C Virus: "Toward Elimination of HCV: How to Get There"

۲

Michael L Cheng BSc^{1,2}, Mohamed S Abdel-Hakeem PhD^{3,4}, Sophie E Cousineau BSc⁵, Jason Grebely PhD⁶, Alison D Marshall MA⁶, Sahar Saeed MSc⁷, Selena M Sagan PhD^{5,8}, Naglaa H Shoukry PhD⁹, Jordan J Feld MD MPH¹⁰, Sonya A MacParland PhD^{1,2}; on behalf of the Canadian Network on Hepatitis C (CanHepC)

ABSTRACT

Hepatitis C virus (HCV) affects more than 268,000 people in Canada. Both the Canadian Institutes of Health Research and the Public Health Agency of Canada recognize the significant impact of HCV-related liver diseases and supported the establishment of a national hepatitis C research network, the Canadian Network on Hepatitis C (CanHepC). Interferon-free direct-acting antiviral regimens lead to more than 95% cure rates in almost all patients with well-tolerated short-course therapy. However, the goal of eliminating HCV in Canada cannot be fully realized until we overcome the financial, geographical, cultural, and social barriers that affect the entire continuum of care from diagnosis and linkage to care through treatment and prevention of new and reinfections. Current practices face difficulties in reversing HCV-induced immunological defects, expanding treatment to neglected communities, combating reinfections and co-infections, and expediting and simplifying the processes of diagnosis and treatment. As part of its knowledge translation mandate, CanHepC has organized the annual Canadian symposium on hepatitis C since 2012. The theme of this year's symposium, "Toward Elimination of HCV: How to Get There?" focused on identifying the requirements of our therapeutic strategies and health policies for the elimination of HCV in Canada.

KEYWORDS: behavioural; biomedical; CanHepC; clinical; epidemiological; hepatitis C virus; NCRTP-HepC; public health; social sciences; viral hepatitis

Author Affiliation

¹Multi-Organ Transplant Program, University Health Network, Toronto, Ontario; ²Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario; ³Penn Institute for Immunology, Department of Microbiology, University of Pennsylvania, Philadelphia, Pennsylvania; ⁴Department of Microbiology and Immunology, Faculty of Pharmacy, Cairo University, Cairo, Egypt; ⁵Department of Microbiology and Immunology, McGill University, Montreal, Quebec; ⁶Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia; ⁷Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec; ⁸Department of Biochemistry, McGill University, Montreal, Quebec; ⁹Centre de Recherche du Centre hospitalier de l'Université de Montréal, Montreal, Quebec; ¹⁰Toronto Centre for Liver Disease, Toronto General Hospital, Toronto, Ontario

Correspondence: Dr Sonya A. MacParland, Department of Laboratory Medicine and Pathobiology, University of Toronto, 101 College Street, Room 3–302, Toronto, ON M5G 1L7. Telephone: 416-581-7630. Fax: 416-581-7515. E-mail: s.macparland@utoronto.ca



Canadian Liver Journal advance online article doi: 10.3138/canlivj.2018-0018 This advance online version may differ slightly from the final published version.

INTRODUCTION

In Canada, morbidity and mortality related to hepatitis C virus (HCV) infection is rising as a result of the large population of people living with HCV (more than 268,000), an aging population with HCV, low uptake of interferon-based therapy (1%–2% per year, limited by side effects), and suboptimal treatment efficacy of interferon-based therapies (1).

The advent of well-tolerated, simple, short-course direct-acting antiviral (DAA) interferon-free HCV regimens with cure rates of more than 95% provide the opportunity to reverse the rising HCV-related morbidity and mortality. However, access and reimbursement for DAA therapies is heterogeneous across provinces and territories in Canada. Although DAA therapies were initially restricted to people with advanced liver disease (stage F2 or greater; 2), the majority of provinces and territories (including Alberta, British Columbia, Manitoba, Prince Edward Island, Ontario, Quebec, Saskatchewan, and Yukon) have removed all restrictions, enabling access for all. However, financial, geographical, cultural, systematic, and social barriers still remain and impair access to testing and treatment in Canada (3). Because of this, prevention strategies, including treatment as prevention or vaccine development, remain important goals.

This commentary is a summary of the 7th Canadian Symposium on Hepatitis C Virus (CSHCV), titled "Toward Elimination of HCV: How to Get There" and focused on identifying strategies to advance prevention, diagnosis, and treatment with the goal of achieving HCV elimination in Canada. This symposium marked the beginning of the inaugural Canadian Liver Meeting, held jointly by the Canadian Network on Hepatitis C (CanHepC), the Canadian Association for the Study of Liver, and the Canadian Association of Hepatology Nurses, with the aim of fostering knowledge exchange on liver disease among researchers, practitioners, policy-makers, and affected communities.

CANADIAN NETWORK ON HEPATITIS C

In 2014, the Canadian Institutes of Health Research (CIHR) and Public Health Agency of Canada (PHAC), with the help of non-governmental (eg, the Canadian Liver Foundation), industry, and private organizations, announced their intention of supporting a National Hepatitis C Research

Network, building on the success of their prior investment with the National CIHR Research Training Program in Hepatitis C (NCRTP-HepC). CanHepC was born from this initiative in July 2015, expanding its training mandate under the NCRTP-HepC program to constitute the first National Collaborative Research Network dedicated to translational research and linking nearly 100 researchers, trainees, and knowledge users (community members, community-based organizations, policy- and decision-makers) in the field of HCV across Canada. The overarching goal of this network is to build research capacity, conduct innovative research, translate evidence into practice and policy, improve HCV prevention and health outcomes of Canadians, and contribute to the global effort to reduce HCV burden by focusing on the themes of prevention, treatment, and outcomes.

CanHepC is built around research cores spanning the four CIHR health research pillars: biomedical discovery research; clinical and research; health services research; and social, cultural, environmental, and population health research. The identified priorities include the development and testing of HCV vaccines, increased testing and identification of infected individuals among vulnerable populations, development of strategies to increase access and adherence to treatment, and generation of evidence-based strategies for models of care and cost effectiveness in HCV treatment. The four research cores are tightly integrated through harmonized resources and infrastructure and both steering and scientific committees. In addition, a knowledge translation and implementation core works as a two-way street to enable the integration of new knowledge in affected communities while informing research about the current realities facing HCV patients and health care systems.

CanHepC continues to run a national training and mentorship program focused on transdisciplinary research on HCV infection. Since 2015, 23 graduate students, 14 postdoctoral fellows, and 25 summer students have been mentored by 1 of the 68 CanHepC-approved mentors from across Canada in alignment with the objectives of CanHepC's four research cores. In addition to their own HCV-related research projects, trainees participate in a weekly seminar series hosted by CanHepC mentors or invited guests, present and discuss journal club papers, participate in knowledge translation with the community, attend and participate in national and

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001

()

international HCV conferences, and participate in grant writing exercises. This program has a total of 71 alumni who have been trained by the program. Several past trainees have come full circle and now represent the next wave of young investigators and mentors within the CanHepC program. To this end, the program has been a major success.

In addition to training the next generation of researchers, CanHepC is in a unique position to establish transversal platforms (for data collection, clinical networks, and linkage) that will be nodes for transdisciplinary collaboration. With this mandate, CanHepC hosted the 7th CSHCV.

THE 7TH CANADIAN SYMPOSIUM ON HEPATITIS C VIRUS

The Canadian HCV research community has facilitated HCV research translation in Canada by organizing the past seven annual Canadian Symposia on Hepatitis C Virus (4–7). The 7th CSHCV marked the first joint conference between CSHCV and the Canadian Liver Meeting. The specific aims of the 7th CSHCV were as follows:

- 1. Biomedical research
 - to review the current understanding of HCV biomedical research
 - to address future challenges in biomedical HCV research
- 2. Social, cultural, environmental, and population health research
 - to review the current epidemiology and the social determinants of health that affect HCV transmission
 - to identify strategies to overcome barriers to HCV control in marginalized populations
- 3. Clinical research
 - to assess the remaining gaps in HCV therapy from diagnosis to linkage to care and treatment
 - to appreciate the benefits of HCV therapy in different real-world population cohorts, particularly in harder-to-reach groups
- 4. Health service delivery:
 - to understand the remaining challenges in HCV-related health service delivery
 - to identify novel models of care for optimizing HCV service delivery

A 1-day symposium was held on February 9, 2018, in Toronto. The theme of the symposium was "Towards Elimination of HCV: How to Get

۲

There" and focused on strategies to promote HCV elimination through diagnosis and treatment of HCV-infected individuals of diverse backgrounds highly effective antiviral using therapies. The symposium included content on topics spanning the four CIHR pillars and provided a multidisciplinary view of the current state of HCV research, treatment, and disease burden relevant to policy formulation both nationally and internationally. The symposium brought together transdisciplinary research scientists, clinicians, nurses, community health workers, patient advocates, community members, and public health officials to discuss future HCV research and care priorities in Canada. All presentations from this and prior symposia are available on the CanHepC YouTube channel (https://www.youtube.com/ channel/UCUgCySYhpXIUuqiaQS_rGJw).

Research gaps in the biomedical sciences: immune recovery after HCV therapy

As components of the adaptive immune system, T cells play a key role in clearing viral infections and establishing an immune memory against pathogens (8). However, these normal functions go awry when the pathogen is not cleared. Chronic viral infections eventually lead to T-cell exhaustion, a phenotype characterized by surface expression of inhibitory receptors and a reduction in T-cell functionality (9).

Highly effective DAA therapies have turned HCV into the first curable chronic viral infection (10), but it is unclear whether virologic cure is sufficient to reverse this T-cell exhaustion. To address this question, Dr Georg M. Lauer (11; Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts) and colleagues isolated HCV-specific CD8⁺ T cells from the blood of chronically infected patients and characterized these T cells pre- and post-DAA treatment (12). This immune phenotyping revealed that DAA therapy was only able to partially reverse the exhaustion phenotype. Although fewer activation markers and more memory markers were expressed post-DAA treatment, these T cells still expressed inhibitory receptors, albeit at lower levels than the pre-DAA exhausted cells. In all, post-DAA CD8⁺ T cells exhibited a distinct phenotype, intermediate between the phenotype of memory T cells after spontaneously resolved HCV infection and that of exhausted T cells. These results suggest that curing HCV may not be sufficient to reverse all aspects ۲

of CD8⁺ T cell exhaustion, although the exact meaning of these phenotypic changes on T-cell functionality remain to be established and thus will be the subject of future studies. ۲

Because chronic viral infections also contribute to immune aging and senescence, Dr Lisa Barrett (13; Dalhousie University, Halifax, Nova Scotia) argued that HCV infection and DAA therapy could serve as a reversible model for immune aging. To illustrate this point, Dr Barrett discussed two studies characterizing the global immune responses of patients who received DAA therapy after a chronic HCV infection (14). The first study profiled an older cohort of patients who received a ribavirin-containing DAA therapy after longer chronic infections, and the second study involved a younger population who received DAA therapy in the context of a correctional facility after shorter chronic infections. In the first study, phenotypic and functional analysis of the B-cell, T-cell, and natural killer (NK) cell compartments of chronically infected patients revealed that those who achieved a sustained virological response (SVR) had a more robust global immune response than those who relapsed. Although no single cell type was key to preventing relapse, the memory B-cell compartment remained abnormal even after the end of treatment. In contrast, by the end of DAA treatment in the second study, the immune phenotypes of the global B-cell and CD8⁺ T-cell compartments were less skewed than, or no different from, those of uninfected controls. This underlines the importance of both patient age and the duration of chronic infection in imprinting the immune system and suggests that continued study of the immune system as a whole in the context of HCV treatment can provide broader insights into immune aging.

Dr Heiner Wedemeyer (15; Essen University Hospital, Essen, Germany) discussed how HCV cure with DAAs was associated with partial restoration of immune responses, especially T lymphocytes, against HCV and other pathogens such as cytomegalovirus and Epstein-Barr virus (16). However, there is high inter-individual variability (16), and some aspects of immunity do not recover. These aspects include a sustained high level of inflammatory mediators (17) and hepatocellular carcinoma in cirrhotic patients (18). Therefore, Dr Wedemeyer highlighted that longer follow-up periods (2–5 y) are required to ensure full restoration of immunity. Taken together, these studies suggest that chronic HCV infection alters the immune response and that these changes may persist even after a virologic cure. The duration of chronic infection as well as the age of the patient may contribute to this persistence. However, the overall significance of these persistent changes in immune phenotype and function is unclear in the context of other viral infections, immune aging in general, or in the immune response to cancer. As such, future research will be required to help elucidate whether these alterations in the immune response contribute to further liver pathology in patients who have undergone HCV treatment, including cirrhosis, fibrosis, or hepatocellular carcinoma.

Clinical research: real-world effectiveness and challenges for DAA treatment

The era of all-oral DAA therapy has provided enthusiasm for the potential elimination of HCV as a major global public health threat by 2030 (19). However, to achieve HCV elimination in Canada, focused efforts are needed to identify and treat populations with limited access to health services, those with co-infections (eg, HIV infection), or those at risk of infection or reinfection. As highlighted in the basic science session, it is also unknown whether cure with DAAs confers immune restoration and protection from reinfection. Thus, the clinical research session focused on real-world data from several challenging settings.

One major population that may be at risk of HCV infection or reinfection are people who inject drugs (PWID). Dr Arshia Alimohammadi (20; Vancouver Infectious Diseases Centre, Vancouver, British Columbia) showed effectiveness of DAA therapy in PWID in a cohort of 238 HCV-infected patients in Vancouver treated within a multidisciplinary model of care. This study demonstrated a cure (defined by SVR 12 weeks post-therapy) of 94%, despite the fact that all patients had a history of either remote or recent drug use. Strategies to enhance HCV testing, linkage to care, and treatment of PWID will be critical to achieve HCV elimination efforts in Canada. Moreover, among people with ongoing risk behaviours for acquisition of HCV infection and reinfection (such as PWID), it will be critical to ensure that prevention strategies (such as needle and syringe programs and opioid substitution therapy) are widely available to prevent reinfection.

HIV co-infection adds further complexity to efforts to eliminate HCV. Dr Carmine Rossi

۲

(21; Research Institute of the McGill University Health Centre, Montreal, Quebec) highlighted data from 259 HCV-HIV co-infected participants treated with DAAs across six Canadian provinces, and the data demonstrated that 92% were able to achieve HCV clearance. Treatment failure was shown to be mainly associated with uncontrolled HIV, renal impairment, or liver disease. These data are encouraging, given some concerns from people in the field of HIV that perhaps responses to DAA therapy in the real world might not be comparable with those of clinical trials.

HIV and HCV prevalence is higher in Canadian correctional facilities than in the general population (22,23). Dr Nadine Kronfli (24; McGill University, Montreal, Quebec) highlighted missed opportunities for care among the incarcerated population with HIV-HCV co-infection. Comparing individuals with a history of incarceration (n = 951) with those without such a history (n = 478) from the Canadian HIV/HCV Co-infection Cohort, Dr Kronfli noted that patients who have previously been incarcerated are less likely to be on combination antiretroviral therapy and virally suppressed in terms of HIV. Moreover, among HIV-HCV co-infected people, people with a history of incarceration were less likely to receive HCV treatment (adjusted hazard ratio = 0.70). As such, prisons represent a missed opportunity to enhance testing and linkage to care and treatment of HCV and HIV.

To treat patients, one first needs to identify them. A major limitation to HCV elimination is the low level of diagnosis at the population level (25; Figure 1). Dr Jordan Feld (27; University of Toronto, Toronto, Ontario) discussed optimal screening strategies and stressed the need to simplify diagnosis, seize every opportunity to test, and match the suitable diagnostic test to the setting to achieve better screening. This could be facilitated by using a variety of novel, simple, cost-effective tools, such as HCV-core antigen testing and dried blood spot testing (28), in parallel with HCV RNA tests. Dr Feld pointed to one successful example—the use in remote areas and with Indigenous populations of dried blood spots that can be mailed to a laboratory, which also ensures reflex HCV RNA testing for positive HCV antibody results. Current screening strategies can be risk based or population based, and either approach has strengths and weaknesses (29). A risk-based strategy focuses on the diagnosis of people with certain risk factors (eg, people living



The 7th CSHCV

Figure 1: Cascade of care for 715 HCV antibody-positive patients from Cherokee Nation Health Services, October 2012—July 2015

Only fractions of patients are captured in the subsequent stage of care, demonstrating gaps in treatment even with effective therapies

HCV = Hepatitis C virus; SVR = Sustained virologic response. Source: Mera et al. (26), reproduced with permission from Morbidity and Mortality Weekly Report

with HIV), and although this strategy has high yield and low cost, it requires people to be engaged in health care. A population-based strategy focuses on the diagnosis of people in a certain population (eg, baby boomers), and this approach is high in coverage rate and easy to implement. However, the disregard of risk factors in a population-based approach makes it inefficient (low rate of positive tests) and therefore expensive. These two types are not mutually exclusive, and because one size does not fit all, the most appropriate strategies for a local setting need to be tailored to the situation.

Social, cultural, environmental, and population health research

This session began with an overview of health systems and HCV elimination with a presentation titled "Overcoming Challenges through a Micro-Elimination Approach" by Dr Jeffrey Lazarus (30; University of Barcelona, Barcelona, Spain). Dr Lazarus described the World Health Organization's (WHO's) goal of eliminating HCV as a major global public health threat as challenging, costly, and complex, but feasible (19; Figure 2, Figure 3, Table 1). Given the daunting task of identifying and treating millions of people chronically infected with HCV globally, one pragmatic approach is to focus on micro-elimination, targeting specific populations. This concept was successful with poliomyelitis and certain key populations infected with HIV. The idea of micro-elimination is to focus national elimination goals on specific subgroups

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001

ML Cheng, MS Abdel-Hakeem, SE Cousineau, et al.



۲

Figure 2: World Health Organization framework for the global health sector strategy on viral hepatitis, 2016–2021

This strategy outlines the contribution from the health sector in combating viral hepatitis and contextualizes the response to viral hepatitis in terms of universal health coverage, one of the goals in the 2030 Agenda for Sustainable Development. Source: Reproduced with permission of the World Health Organization (19).

6 Canadian Liver Journal

۲



۲

Figure 3: World Health Organization 2020 and 2030 targets for the reduction of chronic viral hepatitis B and C infection In 2020, a 30% reduction in new infections and a 0% reduction in deaths are set for hepatitis B and C. The two reductions will be increased to 90% and 65%, respectively, by 2030. Detailed goals are outlined in Table 1. Source: Reproduced with permission from the World Health Organization (19)

Table 1: Detailed summary of the 2020 and 2030 WHO targets for the reduction of chronic viral hepatitis B and C infections

Target Area	Baseline 2015	2020 Targets	2030 Targets
Impact targets			
Incidence: new cases of chronic viral hepatitis B and C infections	Between 6 and 10 million infections are reduced to 0.9 million infections by 2030 (95% decline in hepatitis B virus infections, 80% decline in hepatitis C virus infections)	30% reduction (equivalent to 1% prevalence of HBsAg among children)	90% reduction (equivalent to 0.1% prevalence of HBsAg among children)
Mortality: viral hepatitis B and C deaths	1.4 million deaths reduced to fewer than 500,000 by 2030 (65% for both viral hepatitis B and C)	10% reduction	65% reduction
Service coverage targets			
Viral hepatitis B and C diagnosis	<5% of chronic hepatitis infections diagnosed	30%	90%
Viral hepatitis B and C treatment	<1% receiving treatment	 5 million people will be receiving hepatitis B virus treatment 3 million people have received hepatitis C virus treatment (Both targets are cumulative by 2020) 	80% of eligible persons with chronic hepatitis B virus infection treated 80% of eligible persons with chronic hepatitis C virus infection treated

Note: The 2020 target of 1% HBsAg prevalence in children is a global average; regional WHO committees may have region-specific targets. WHO also noted that the 2030 target of 0.1% HBsAg prevalence in children requires the development of new validation methods.

WHO = World Health Organization; HBsAg: Hepatitis B virus surface antigen Source: Reproduced with permission from the World Health Organization (19).

Canadian Liver Journal 7

2018-0018 MacParland.indd 7

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001

9/7/18 6:15 PM

۲

(eg, people living with HIV, prisoners, people with hemophilia, children), settings (hospitals, addiction centres), generational cohorts (baby boomers), or geographic areas (cities, regions) for which treatment and prevention interventions can be delivered and monitored more efficiently and effectively using targeted methods (31). Dr Lazarus described micro-elimination as achievable, realistic, and pragmatic, which can provide important political capital by showing policy-makers that when adequate health system resources are invested, HCV infection becomes a conquerable disease.

In Canada, Indigenous people have been disproportionately affected by HCV infection. Dr Jennifer Walker (32; Laurentian University, Sudbury, Ontario) presented on the Indigenous perspectives on health and wellness and Indigenous data sovereignty and research ethics. Dr Walker noted the complexity of health and the perspectives of health and well-being from Indigenous communities. She introduced two frameworks that are important when thinking about Indigenous health, specifically in the context of HCV. First, she introduced the idea of well-being as the total health of the total person in the total environment. This multifaceted concept includes mental, physical, and spiritual aspects of wellbeing for an Indigenous person (33). Second, she explained the determinants of Indigenous health, which go beyond traditional social determinants of health to include proximal, intermediate, and distal components (34). She explained how distal determinants of Indigenous health (eg, colonialism and racism) cannot be ignored in the context of policies, research, or care of HCV because such a high proportion of Indigenous people are infected with HCV. She continued to explain how there is an increased interest in principles of Indigenous data sovereignty, as established by the Indigenous people in Canada and internationally (35). Understanding these principles and their practical application in health care, research, and surveillance is important for researchers to ensure that international and Canadian standards for Indigenous rights and ethical research are upheld.

The Social, Cultural, Environmental, and Population Health Research Section continued with the "Nothing About Us Without Us" panel introduced by Suzanne Fish (36) from Canadian AIDS Treatment Information Exchange (CATIE; Toronto, Ontario). CATIE is a national organization that conducts knowledge exchange with and for community service providers. Lindsay Jennings from Prison HIV/AIDS Support Action Network (Toronto, Ontario) emphasized the challenges of managing HCV in a prison setting, specifically in regard to accessing treatment and harm reduction strategies. Shujaat Hussain (CATIE, Toronto, Ontario) furthered the discussion of engaging people in HCV treatment from the perspective of newcomers in Canada. As an immigrant, Mr. Hussain recounted his experience from diagnosis to cure of hepatitis C in Canada. His personal story put the disease in the context of his cultural background, where the importance of liver health may not be prioritized. Ms Jennings and Mr. Hussain demonstrated the value and importance of engaging people with lived experience at every stage of HCV programming, policy, and research.

Communities in remote regions of Canada face unique challenges for HCV elimination. Dustin Dapp (37; Simon Fraser University, Burnaby, British Columbia) and Lucy Newman-Hogan (University of Guelph, Guelph, Ontario) identified financial and geographical barriers for health care providers working in remote areas, as well as their lack of cultural and safety trainings. To effectively deliver care to these communities, better understanding of and integration into local culture is essential to build trust and reduce stigma.

This panel concluded with Fozia Tanveer (38; CATIE, Toronto, Ontario) with a focus on hepatitis C education for immigrants and newcomers. Ms Tanveer outlined CATIE's Ontario Hepatitis C Education and Outreach Program with Immigrants and Newcomers initiative, where hepatitis C education is linguistically and culturally adapted to the largest groups of immigrants in Canada: Filipino, Punjabi, Chinese, and Pakistani (39). Ms Tanveer pointed out the success of this program, in which 89% of participants reported an increase in knowledge. CATIE plans to expand the program to the rest of Ontario and provide relevant resources for frontline workers.

Health services research

Most countries worldwide are not on track to achieve the WHO targets of eliminating HCV infection as a major public health threat by 2030, including Canada (40; Figure 4). Advances in basic science research, clinical care, and understanding of cultural and social perspectives cannot be directly translated to HCV elimination goals without also

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001





A: Progress of countries in terms of achieving the elimination targets of HCV by 2030 as set by the World Health Organization. Only nine countries are currently on track: Australia, Egypt, France, Georgia, Germany, Iceland, Japan, Netherlands, and Qatar. B: Number of predicted incidents of viremic HCV infection (based on 2016 data; 41) and WHO targets for countries at various stages of progress toward HCV elimination. In Cameroon, HCV elimination is unachievable given present policy. Canada is working toward elimination. Australia is on track for WHO elimination targets. WHO = World Health Organization; HCV = Hepatitis C virus

۲

Source: Reproduced with permission from the Center for Disease Analysis Foundation (40).

overcoming barriers in health services. Dr Homie Razavi (42; Center for Disease Analysis, Lafayette, Colorado) presented on why governments can be hesitant to invest in HCV health services: over-evaluation of risks. In spite of the perceived risks, however, Dr Razavi demonstrated—via modelling analyses from multiple countries (41) that upfront financial investment in HCV-related services and care will ultimately be cost-saving and elicit positive returns (43). Given this, Dr Razavi emphasized that researchers should present policymakers with evidence that demonstrates gains in HCV investment (eg, lives saved, transplants averted, less health care spending) rather than losses.

Improvements in health services to address HCV infection will also require a better understanding of the populations affected. Dr Naveed Janjua (44;

University of British Columbia, Vancouver, British Columbia) highlighted that strategies to target birth cohort populations (the baby boomer cohort of people born between 1945 and 1965)-who largely acquired HCV infection through iatrogenic transmission or through former injection drug use-will differ from approaches aimed at younger cohorts with recent injection drug use (45). People with ongoing injection drug use risk behaviours (viz. needle and syringe sharing) are at an increased risk of HCV transmission. Hence, a two-pronged approach will be needed to ensure that there is enhanced treatment among older populations (to reduce the rising burden of advanced liver disease) and younger people who inject drugs (to reduce ongoing HCV transmission). People with ongoing injection drug use are also at an increased risk for social vulnerabilities, drug-related harm, and other

comorbidities (eg, drug use, alcohol use, mental illness, and co-infection). As such, it is critical to address the social determinants of health (including homelessness and poverty) as part of the overall strategy to address HCV infection in Canada.

National HCV strategies

PHAC is currently developing a National Sexually Transmitted and Blood-borne Infections (STBBI) framework, which includes a focus on HCV infection. A presentation by CanHepC trainee Alison Marshall (46; University of New South Wales, Sydney, New South Wales) highlighted that Canada is well positioned to implement activities set by WHO to eliminate HCV infection as a major public health threat by 2030 given that Canada's core health values are aligned with WHO's (ie, providing services within a universal health coverage framework, offering a continuum of health services, and using a public health approach; 19). Drawing from WHO documentation, Ms Marshall emphasized how national plans can help to outline HCV priorities, actions, and respective roles; direct resources and measure progress; minimize intracountry disparities in health services; and provide a reference for provinces and territories to create regional plans (19, 47, 48). Ms Marshall then signified the role of a research framework (and how researchers can assist PHAC) to help inform the STBBI strategy. Specifically, Ms Marshall affirmed the need to conduct a WHO 'situation analysis' by identifying persons affected by viral hepatitis (eg, priority populations), timing of infection (eg, age cohorts), locations (eg, geographical regions), and how persons are affected (eg, impact of infection) in Canada (47). Last, as emphasized in the presentation, the CanHepC Network looks forward to working with PHAC to develop a document that helps with implementation of the STBBI framework to help ensure that Canada is on track for elimination of HCV infection as a major public health threat in Canada by 2030.

This joint symposium transitioned from the CSHCV to the Canadian Liver Meeting with a presentation by Dr Ricardo Baptista Leite (49; Member of Parliament and infectious disease physician, Lisbon, Portugal), who provided some insight into HCV policy development in Portugal. In 2015, the Ministry of Health in Portugal agreed to universal DAA access under the following arrangement: a risk-sharing model, payments made on a centralized system, and a volume-based

agreement with pharmaceutical companies. A national HCV action plan and treatment guidelines are currently in development. In Portugal, approximately 17,600 persons have been diagnosed (of an estimated 60,000-80,000 persons with HCV infection), of whom approximately 12,400 have commenced treatment and approximately 6,600 have been cured. More important, Dr Leite elucidated some strategies for researchers and community groups to consider when working with decision-makers: (1) communicate how the information presented agrees with public concerns, (2) show before and after data, (3) demonstrate cost savings, and (4) present timely results. Dr Leite concluded the talk by emphasizing that effective policy change requires evidence-based, datadriven, and decision-oriented policy-making. By satisfying these criteria, it is possible for Canada to adopt a national strategy that leads to improved health and care while also reducing cost.

Outcomes of the 7th Canadian Symposium on Hepatitis C Virus

With the wide availability of DAA therapies, elimination of HCV as a major public health threat in Canada becomes a feasible target, and the 7th CSHCV identified the requirements and remaining steps while highlighting current barriers in various disciplines. The Basic Science session underscored the gaps in research on immune aging and immune alterations that persist after virologic cure. The presentations in the Social, Cultural, Environmental, and Population Health Research session concluded that policies regarding eliminating HCV in subpopulations (e.g., Indigenous persons and incarcerated individuals) need to be contextualized and humanized to achieve their full potential. In addition, the Clinical Research session suggests PWID and HIV-HCV co-infected patients as key cohorts for targeted HCV elimination. Clinical researchers also recommend longer follow-up periods to ensure complete immune restoration as well as more efficient diagnostic tools. The Health Services Research session supplemented these recommendations by emphasizing the need for better communication with policy-makers and inclusion of younger cohorts in our studies.

To combat these multifaceted problems at various fronts with the goal of HCV elimination, the solutions need to be equally diverse and collaborative. The framework outlined by Alison Marshall and the Portugal's national HCV

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001

۲

action demonstrate how research findings can be effectively translated into potent health policies. These policies can be further augmented by a program that also considers comorbidities, loss of patients throughout the cascade of care, and cultural differences in Canadian subpopulations. By incorporating the progress of previous symposia and continuing multidisciplinary discussions, this symposium lays the foundation for Canada to gain traction in realizing the WHO targets to eliminate HCV by 2030.

ACKNOWLEDGEMENTS: The CanHepC Mentors: Michel Alary (Centre de recherche du CHU de Québec), Dan Allman (University of Toronto), Fernando Alverez (CHU Sainte-Justine), Louise Balfour (The Ottawa Hospital), Lisa Barrett (Nova Scotia Health Authority/Dalhousie University), Marc Bilodeau (Université de Montréal), Julie Bruneau (Université de Montréal), Carla Coffin (University of Calgary), Brian Conway (Vancouver Infectious Diseases Centre), Curtis Cooper (University of Ottawa), Angela Crawley (University of Ottawa), Jordan Feld (University Health Network), Benedickt Fischer (Centre for Addiction and Mental Health), Jennifer Flemming (Queen's University), Mattias Götte (University of Alberta), Jason Grebely (University of New South Wales Australia), Christina Greenaway (McGill University), Kanna Hayashi (University of British Columbia), Michael Houghton (University of Alberta), Anita Howe (University of British Columbia), Naveed Safar Janjua (University of British Columbia), Didier Jutras-Aswad (Université de Montréal), Thomas Kerr (University of British Columbia), Alexandra King (University of Saskatchewan), Marina Klein (McGill University), Norman Kneteman (University of Alberta), Murray Krahn (University of Toronto), Mel Krajden (University of British Columbia), Jeff Kwong (University of Toronto), Alain Lamarre (Institut National de la Recherche Scientifique-Institut Armand Frappier), Daniel Lamarre (Université de Montréal), Samuel Lee (University of Calgary), Seung-Hwan Lee (University of Ottawa), Simon Ling (University of Toronto), Qiang Liu (University of Saskatchewan), Sonya MacParland (University of Toronto), Valérie Martel-Laferrière (Centre de recherche du CHUM), Andrew Mason (University of Alberta), Ian McGilvray (University of Toronto), Thomas Michalak (Memorial University), M-J Milloy (University of British Columbia), Gerry

Mugford (Memorial University), Mario Ostrowski (University of Toronto), John Pezacki (University of Ottawa), Chris Richarson (Dalhousie University), Eve Roberts (University of Toronto), Elise Roy (Université de Sherbrooke), Rod Russell (Memorial University), Selena Sagan (McGill University), Beate Sander (University of Toronto), Luis Schang (University of Alberta), Dena Schanzer (Public Health Agency of Canada), Giada Sebastiani (McGill University), Nazia Selzner (Toronto General Hospital), Morris Sherman (University Health Network), Naglaa Shoukry (Université de Montréal), Daniel Smyth (Dalhousie University), Hugo Soudeyns (Université de Montréal), Rosie Thein (University of Toronto), Mark Tyndall (University of British Columbia), Lorne Tyrrell (University of Alberta), Marie-Louise Vachon (Université Laval), Joyce Wilson (University of Saskatchewan), Wendy Wobeser (Queen's University), William Wong (University of Toronto), and Eric Yoshida (University of British Columbia). The Knowledge Users: Anis Aslam (University of British Columbia), Melisa Dickie (Canadian AIDS Treatment Information Exchange), Gary Fagan (Canadian Liver Foundation), Janet Hatcher Roberts (Canadian Society for International Health), Bonnie Henry (BC Ministry of Health), Daryl Luster (Pacific HepC Network), Renee Masching (Canadian Aboriginal AIDS Network), Denise Thomas (Canadian Association of Hepatology Nurses), Claire Wartelle (Centre de Recherche du CHUM). The CanHepC Trainees: Mohamed Abdel-Hakeem (University of Pennsylvania), Christopher Ablenas (McGill University), Faria Ahmed (University of Ottawa), Yalena Amador-Canizares (University of Saskatchewan), Adelina Artenie (McGill University), Jacqueline Barry (Memorial University), Annie Bernier (McGill University), Justin Chan (Massachusetts General Hospital), Che Colpitts (University College London), Sophie Cousineau (McGill University), Evan Cunningham (University of New South Wales), Maryam Darvishian (University of British Columbia), Aysegul Erman (University of Toronto), Thomas Fabre (Université de Montréal), Brendan Jacka (Université de Montréal), Gillian Kolla (University of Toronto), Rasika Kunden (University of Saskatchewan), Ching-Hsuan Liu (Dalhousie University), Alison Marshall (University of New South Wales Australia), Sabrina Mazouz (Université de Montréal), Andrew Mendlowitz (University of Toronto), Nanor Minoyan (Université de Montréal),

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001

۲

Armstrong Murira (Institut Armand Frappier), Megan Powdrill (University of Ottawa), Carmine Rossi (University of British Columbia), Yasmin Saeed (University of Toronto), Sahar Saeed (McGill University), Abdool Shafaaz Yasseen (University of Toronto). Lay Member: Frank Bialystock (University of Toronto).

FUNDING: CanHepC is funded by a joint initiative of the Canadian Institutes of Health Research (CIHR; NHC-142832), a network grant from CIHR (Grant Number NHC-142832), and the Public Health Agency of Canada (PHAC). In addition, CanHepC has received funding for the training program from Abbvie, Gilead, and Merck. The 7th Canadian Symposium on Hepatitis C Virus was supported by CIHR (PCS-392522). Additional funding was provided by Abbvie, Gilead, and Merck through the Canadian Liver Meeting and by Réseau Sida. The views expressed in this publication do not necessarily represent the position of the Australian Government. Jason Grebely is supported through a National Health and Medical Research Council Career Development Fellowship. The views expressed in this publication are those of the authors and do not reflect the position of the CIHR, PHAC, the Australian Government, or other sources of funding.

DISCLOSURES: The authors have nothing to disclose.

REFERENCES

- Myers RP, Krajden M, Bilodeau M, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol. 2014;28(5):243–50. https://doi.org/ 10.1155/2014/317623. Medline:24839620
- MarshallAD,SaeedS,BarrettL,etal.;Canadian Network on Hepatitis C. Restrictions for reimbursement of direct-acting antiviral treatment for hepatitis C virus infection in Canada: a descriptive study. CMAJ Open. 2016;4(4):E605–14. https://doi.org/10.9778/ cmajo.20160008. Medline:28018873
- Dore GJ, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden. J Viral Hepat. 2014;21(Suppl 1):1–4. https:// doi.org/10.1111/jvh.12253. Medline:24713003
- Grebely J, Bilodeau M, Feld JJ, et al; National CIHR Research Training Program in Hepatitis
 The Second Canadian Symposium on Hepatitis C Virus: a call to action. Can J
- 12 Canadian Liver Journal

Gastroenterol.2013;27(11):627–32.https://doi .org/10.1155/2013/242405.Medline:24199209

- MacParland SA, Bilodeau M, Grebely J, et al.; National CIHR Research Training Program in Hepatitis C. The 3rd Canadian Symposium on Hepatitis C Virus: expanding care in the interferon-free era. Can J Gastroenterol Hepatol. 2014;28(9):481–7. https://doi.org/ 10.1155/2014/704919. Medline:25314353
- 6. Sagan SM, Dupont B, Grebely J, et al. Highlights of the Fourth Canadian Symposium on Hepatitis C: Moving towards a national action plan. Can J Gastroenterol Hepatol. 2016;2016:5743521.
- van Buuren N, Fradette L, Grebely J, et al. The 5th Canadian Symposium on Hepatitis C Virus: we are not done yet—remaining challenges in hepatitis C. Can J Gastroenterol Hepatol. 2016;2016:7603526. https://doi.org/ 10.1155/2016/7603526. Medline:27843889
- Laidlaw BJ, Craft JE, Kaech SM. The multifaceted role of CD4(+) T cells in CD8(+) T cell memory. Nat Rev Immunol. 2016;16(2):102–11. https://doi.org/10.1038/ nri.2015.10. Medline:26781939
- Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature. 2006;443(7109):350–4. https://doi .org/10.1038/nature05115. Medline:16921384
- Pawlotsky JM, Feld JJ, Zeuzem S, et al. From non-A, non-B hepatitis to hepatitis C virus cure. J Hepatol. 2015;62(1 Suppl):S87–99. https://doi.org/10.1016/j.jhep.2015.02.006. Medline:25920094
- 11. Lauer G, ed. Reinfection with hepatitis C virus—T cells to the rescue? Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 12. Wolski D, Foote PK, Chen DY, et al. Early transcriptional divergence marks virus-specific primary human CD8+ T cells in chronic versus acuteinfection. Immunity. 2017;47(4):648–663.e8. https://doi.org/10.1016/j.immuni.2017.09.006. Medline:29045899
- 13. Barrett L, ed. DAA-induced reversal of immune senescence. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.

۲

14. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013;310(8):804–11. https://doi.org/10.1001/jama.2013.109309. Medline:23982366 ۲

- 15. Wedemeyer H, ed. NK cell and T cell function during and after HCV. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 16. Owusu Sekyere S, Suneetha PV, Hardtke S, et al. Type I interferon elevates co-regulatory receptor expression on CMV- and EBV-specific CD8 T cells in chronic hepatitis C. Front Immunol.2015;6:270.https://doi.org/10.3389/ fimmu.2015.00270. Medline:26113847
- 17. Hengst J, Falk CS, Schlaphoff V, et al. Directacting antiviral-induced hepatitis C virus clearance does not completely restore the altered cytokine and chemokine milieu in patients with chronic hepatitis C. J Infect Dis. 2016;214(12):1965–74. https://doi.org/10.1093/ infdis/jiw457. Medline:27683821
- 18. Mettke F, Schlevogt B, Deterding K, et al. Interferon-free therapy of chronic hepatitis C with direct-acting antivirals does not change the short-term risk for de novo hepatocellular carcinoma in patients with liver cirrhosis. Aliment Pharmacol Ther. 2018;47(4):516–25. https:// doi.org/10.1111/apt.14427. Medline:29205405
- 19. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021: Towards ending viral hepatitis. www.who. int/hepatitis/strategy2016-2021/ghss-hep/en/ (Accessed May 21, 2017).
- 20. Alimohammadi A, ed. All-oral anti-HCV therapy in injection drug users: updated real world data. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 21. Rossi C, ed. Real-world effectiveness of interferon-free, all-oral direct-acting antivirals in the setting of hepatitis C and HIV coinfection. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 22. Canadian AIDS Treatment Information Exchange. HIV in Canada: a primer for service

providers. www.catie.ca/en/hiv-canada/2/ 2-3/2-3-8 (Accessed February 1, 2018).

- 23. Challacombe L. The epidemiology of hepatitis C in Canada. http://www.catie.ca/en/ fact-sheets/epidemiology/epidemiologyhepatitis-c-canada (Accessed February 9, 2018).
- 24. Kronfli N, ed. Decreased hepatitis C (HCV) treatment uptake among HIV-HCV co-infected patients with a history of incarceration: missed opportunities for care. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 25. Bruggmann P, Berg T, Øvrehus AL, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat. 2014;21(Suppl 1):5–33. https://doi. org/10.1111/jvh.12247. Medline:24713004
- 26. Mera J, Vellozzi C, Hariri S, et al. Identification and clinical management of persons with chronic hepatitis C virus infection—Cherokee Nation, 2012–2015. MMWR Morb Mortal Wkly Rep. 2016;65(18):461–6. https://doi.org/10.15585/ mmwr.mm6518a2. Medline:27172175
- 27. Feld J, ed. Optimal screening strategies: it's all about the local situation. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- Soulier A, Poiteau L, Rosa I, et al. Dried blood spots: a tool to ensure broad access to hepatitis C screening, diagnosis, and treatment monitoring. J Infect Dis. 2016;213(7):1087–95. https://doi .org/10.1093/infdis/jiv423. Medline:26333945
- 29. Bolotin S, Feld JJ, Garber G, et al. Populationbased estimate of hepatitis C virus prevalence in Ontario, Canada. PLoS One. 2018;13(1):e0191184.https://doi.org/10.1371/ journal.pone.0191184. Medline:29360823
- 30. Lazarus J, ed. Health systems and HCV elimination: overcoming challenges through a micro-elimination approach. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 31. Lazarus JV, Wiktor S, Colombo M, et al.; EASL International Liver Foundation. Microelimination—A path to global elimination of hepatitis C. J Hepatol. 2017;67(4):665–6. https://doi.org/10.1016/j.jhep.2017.06.033. Medline:28760329

\${protocol}://canlivj.utpjournals.press/doi/pdf/10.3138/canlivj.2018-001

32. Walker J, ed. Indigenous data sovereignty on the path to HCV elimination. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada. ۲

- 33. First Nations Information Governance Centre. First Nations Regional Longitudinal Health Survey. fnigc.ca/sites/default/files/ENpdf/ RHS_2002/rhs2002-03-technical_report.pdf (Accessed February 1, 2018).
- 34. Reading C. Structural determinants of Aboriginal peoples' health. In: Greenwood M, de Leeuw S, Lindsay NM, et al. (eds.) Determinants of Indigenous peoples' health in Canada: beyond the social. Toronto: Canadian Scholars Press; 2015. p. 1–15.
- 35. Walker J, Lovett R, Kukutai T, et al. Indigenous health data and the path to healing. Lancet. 2017;390(10107):2022–3. https:// doi.org/10.1016/S0140-6736(17)32755-1. Medline:29115232
- 36. Jennings L, Hussain S, Fish S, eds. Nothing about us without us: the value of engaging people with lived experience of HCV in all areas of the HCV response. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 37. Dapp D, Newman-Hogan L, eds. HCV: bringing care to patients in rural and remote settings. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 38. Tanveer F, ed. Ontario Hepatitis C Education and Outreach Program with immigrants and newcomers. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 39. Immigration, Refugees and Citizenship Canada. Annual Report to Parliament on Immigration, 2016. https://www.canada. ca/en/immigration-refugees-citizenship/ corporate/publications-manuals/annualreport-parliament-immigration-2016.html (Accessed July 27, 2018).
- 40. CDA Foundation, Polaris Observatory. Hepatitis C—Canada. http://cdafound.org/ polaris/ (Accessed February 1, 2018).
- 41. Razavi H, Waked I, Sarrazin C, et al. The present and future disease burden of hepatitis

Cvirus (HCV) infection with today's treatment paradigm. J Viral Hepat. 2014;21(Suppl 1): 34–59. https://doi.org/10.1111/jvh.12248. Medline:24713005

- 42. Razavi H, ed. Use of data to drive global policy to eliminate HCV. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 43. RazaviH, RobbinsS, ZeuzemS, etal.; European Union HCV Collaborators. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(5):325–36. https://doi.org/10.1016/ S2468-1253(17)30045-6. Medline:28397696
- 44. Janjua N, ed. What is needed to eliminate hepatitis C in Canada? Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 45. Janjua NZ, Yu A, Kuo M, et al. Twin epidemics of new and prevalent hepatitis C infections in Canada: BC Hepatitis Testers Cohort. BMC Infect Dis. 2016;16(1):334. https://doi.org/10.1186/s12879-016-1683-z. Medline:27436414
- 46. Marshall A, ed. A framework of a national hepatitis C elimination strategy in Canada. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.
- 47. World Health Organization. Manual for the development and assessment of national viral hepatitis plans: a provisional document. http://www.who.int/hepatitis/publications/ manual-hep-plan/en/ (Accessed July 27, 2018).
- 48. World Health Organization. Monitoring and evaluation for viral hepatitis B and C: Recommended indicators and framework. Technical report. http://www.who.int/ hepatitis/publications/hep-b-c-monitoringevaluation/en/ (Accessed July 27, 2018).
- 49. Baptista Leite R, ed. HCV policy in action: lessons learned from Portugal. Paper presented at: 7th Canadian Symposium on Hepatitis C Virus; February 2018; Toronto, ON, Canada.

14 Canadian Liver Journal

۲