Patient Group Input to CADTH

Section 1 — General Information

Name of the therapeutic review	Direct-Acting Antivirals for Chronic Hepatitis C Genotype 1
Name of patient group	Canadian Treatment Action Council (CTAC)
Patient group's contact information	555 Richmond St. W, Suite 612. Toronto, ON M5V3B1 416.410.6538 www.ctac.ca
Date submitted	March 17, 2015

1.1 Submitting Organization

The Canadian Treatment Action Council (CTAC) is Canada's national non-governmental organization addressing access to treatment, care and support for people living with HIV and hepatitis C. CTAC's organizational goals are to meaningfully engage community members, service providers, policymakers and other relevant stakeholders to identify, develop, and implement policy and program solutions. CTAC understands that treatment access should be considered in its holistic form, encompassing the range of treatment, care and support needs required to reach the most successful treatment experience possible for people living with HIV and/or viral hepatitis co-infection.

Full CTAC membership is reserved for: a) individual people living with HIV (including HCV co-infection); b) organizations, groups or projects with a substantial HIV mandate (including HCV co-infection). Associate CTAC membership is open to any individual, organization, group or project that supports CTAC's mandate and objectives.

1.2 Conflict of Interest Declarations

CTAC received unrestricted organizational and educational grants from the following organizations in the 2013-2014 fiscal year: Abbott/Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen, and ViiV Healthcare.

Section 2 — Condition and Current Therapy Information

2.1 Information Gathering

CTAC routinely conducts national patient consultation webinars to inform stakeholders of new treatment developments. Specifically, CTAC monitors Common Drug Review (CDR) submissions and conducts webinars associated with each application for HIV or HCV health technologies. Following this webinar, attendees participate in a survey. The data from this survey provides the basis for the ensuing Patient Group Input report that CTAC writes and submits to the CDR for their review. Each webinar is recorded and posted to CTAC social media (twitter, facebook, YouTube, etc) where it remains for viewing. The webinar and survey are conducted no less than one full week before the Patient Input Survey's CADTH deadline, and the survey is accessible and open during that time.

CTAC has conducted webinars regarding the CDR submissions for Direct-Acting Antivirals (DAAs) asunaprevir (Feb. 25th, 2015), daclatasvir (Feb. 25th, 2015), sofosbuvir (Oct. 13th, 2013), ledipasvir/sofosbuvir (Sept. 30th, 2014), and ombitasvir/paritaprevir/ritonavir/dasabuvir (Dec.

10th, 2014). These webinars presented and discussed data from clinical trials as well as patient experience where possible. Over these 5 DAA webinars, CTAC enjoyed the participation of 54 attendees. In the ensuing surveys, 25 were completed in full.

Over all webinars, demographic averages were 58% male, median age of 48, with representation from all provinces and one territory (Yukon). In many of the surveys, CTAC enjoyed several patients with treatment experience concerning the drug in question, but more often, respondents were inexperienced to the treatment being reviewed. All patient respondents were able to interact and participate in high-level discussions concerning HCV virology such as sustained-virologic-response, drug-drug interactions, and liver damage scales and measures (metavir, fibroscan, the F-series of liver health). All patients were familiar with pegylated interferon and ribavirin and some had treatment experience with those medications. All patients were familiar with the contemporary pipeline of HCV medications and often framed CDR applications in the context of other available (and in the Canadian context, many *unavailable*) treatments.

Data from these previous patient input submissions has been used to complement this report. In all cases, only data concerning the above mentioned DAAs has been used in this report. Further, this report features not only data from the original reports, but also notes from the consultation discussion and any relevant quotes provided therein.

2.2 Impact of Condition on Patients

Hepatitis C is a serious and life-threatening virus that can impair liver functions, lead to cirrhosis, and is considered the leading cause of hepatocelluar carcinoma. Most recent data from Health Canada suggests that as many as 300,000 Canadians are presently infected with HCV, with as many as 70% of those unaware of their infection and Health Canada data further suggests there are as many as 8,000 new cases annually.

A hearty and unique virus, HCV is transmitted through blood-to-blood contact. While approximately 20% of people infected will pass the virus naturally, approximately 80% will not and the presence of the virus will develop into a chronic HCV infection. Asymptomatic for much of its cycle, HCV infection slowly causes significant liver damage, contributing to fibrosis, cirrhosis, and even liver cancer. Past strategies for treatment suggested a wait-and-see approach to determine if the virus was passed naturally, or to confirm that liver damage progression (fibrosis) was fast and severe enough to demand treatment (metavir score > F2). New evidence, however, suggests that more than 60% of all HCV sufferers will sustain fibrosis and incur liver damage necessitating quick and effective treatment. Left untreated for long periods of time, chronic HCV can lead to decompensated liver cirrhosis or hepatocellular carcinoma, the leading causes of liver transplantation in Canada. Consider the impact of this strategy to special populations in Canada, as one caregiver respondent noted, “As an example, an individual I am working with had taken great strides to achieve stability in her life with the hopes of getting on hepatitis C treatment. She is in supportive housing, and had stopped her substance use. After visiting the hepatitis C clinic and being told she was not eligible because her liver was too healthy, she questioned why she had put all that effort into maintaining sobriety and began her substance use again, putting her housing at risk. She had all the pieces lined up, and would have been in a good spot to initiate treatment, however this news has sent her on a path that may indeed lead to liver damage, but also a more chaotic situation that would not be conducive to an easy treatment for her.”

HCV's often-asymptomatic nature is considered an important variable in its prevalence and spread. Many people live unknowingly with this infection and quietly suffer significant damage. As one HCV sufferer responding to CTAC survey reported, "*I was unaware that I had hepatitis C until 2009, some 30 years after contracting it. It is my understanding that there are ongoing symptoms… but all would have been considered a normal part of my adult life as I was a teenager when I was infected.*" Most people seek diagnosis and treatment when experiencing symptoms of fibrosis, cirrhosis, or severe liver damage, but these symptoms are the result of the infection already being possibly decades old. The respondent continued, "*I was diagnosed with F3 liver damage, so it is reasonable to say that hepatitis C treatment saved my life.*" HCV sufferers do sometimes report impact of their infection or liver damage early, however. Many respondents echoed the remarks of one 52 year-old female from British Columbia, who said her symptoms included "Chronic fatigue, some short-term memory concerns." Both of these symptoms significantly impacted the sufferer's ability to maintain employment or social activities.

Also of interest to CTAC, a significant number of people living with HIV infection are co-infected with HCV. Approximately 13,000 Canadians are co-infected with HIV and HCV. Extrapolating from existing Health Canada data, we can postulate that approximately 20% of all people living HIV would be infected with HCV, and approximately 5% of all people living with HCV would be infected with HIV. Not only do people living with co-infection suffer under increased stigma and differing treatment needs, both viruses exacerbate the progression of the other, and many of their respective medications impact one another. For example, patients using HIV protease inhibitor tipranavir-ritonavir must be careful of possible drug interactions with sofosbuvir-based HCV treatments.

While the Public Health Agency of Canada has suggested that a significant proportion of those infected by HCV are receiving treatment, IMS MIDAS market data publicly reports HCV treatment sales, which suggest that approximately only 10,000 of the suspected 250,000+ are currently being treated. While HCV treatments become more effective and more tolerable, the relative lack of sufferers being treated is a conspicuous and jarring discrepancy.

2.3 Patients' Experiences With Current Therapy

Attendees in the discussion period of the consultation webinars routinely declared experience in service-provision, care-giving, and as patients experiencing therapy for chronic HCV.

CTAC was fortunate to hear the testimony of many treatment-experienced patients who were familiar with many different types of treatment. Without fail, those experienced in pegylated interferon and ribavirin treatments were united in their call for a move away from that standard of treatment. All respondents to all consultation webinars have expressed confidence and enthusiasm that contemporary treatment options appear to be moving away from PEG/RBV and toward more tolerable, shorter-treatment DAAs.

Respondents were able to note increasing returns and efficiency as DAAs progressed from one generation to the next. Even early DAAs like boceprevir and telaprevir (for which CTAC also conducted webinar consultations) were problematic, and next-gen DAAs like simeprevir and sofosbuvir were both evaluated against those predecessors. For example, during our sofosbuvir consultation, one respondent noted that even early DAAs caused significant side effects, specifically fatigue, forcing that patient to live while "*functioning at half of usual level… I can walk but not jog; can only work out every second day. Exhausted most of the time. I have to plan how I spend my energy*."

Respondents were quick to evaluate and discuss side effects and gave positive feedback on the trend of more tolerable treatments as DAAs improved. Perhaps reflective of the upcoming PHAC merger of HIV/HCV community service funds, many respondents were concerned with treatments for those co-infected with HIV and HCV. Patients noted a significant (avg 2.5-3.75 year; boceprevir and telaprevir) gap between testing for HCV mono-infected and HIV/HCV co-infected patients in clinical trial settings. One co-infected patient noted, "*psychological anxiety about my new HCV and co-infection status that I had to deal with… in particular, concerns about the efficacy and side effects of treatment.*"

Our patient respondents also regularly reviewed and evaluated drugs based on their place and context in contemporary HCV treatment. For example, respondents to our HOLKIRA PAK (ombitasvir, paritaprevir, ritonavir, dasabuvir; Abbvie) consultations noted that this treatment was *not* a fixed-dose-combination, single pill, once-daily treatment. This differed from most other treatments available or in development. However, respondents suggested that this was a fine "trade-off" for more tolerable, shorter treatments. In short, HCV patients did not demand single pill regimens, and would accept an increased pill burden if it offered better, faster results. Many patients noted that this was contrary to much pharmaceutical messaging, which suggests lower pill burdens increase adherence, despite length of treatment regimen.

Despite the above, many patient respondents are concerned about the continued use of ribavirin in contemporary clinical trials and treatments. Specifically, respondents were concerned that Ribavirin might be needed for HCV sufferers of Genotype 1A, but not for Genotype 1B (as suggested in asunaprevir, daclatasvir, beclabuvir, and sofosbuvir clinical trial data). Several patients noted that they were discouraged from seeking treatment because of continued presence of ribavirin in contemporary therapy options. At least two respondents called ribavirin "poison."

New DAA treatments promise to shorten treatment duration, increase efficacy and be more tolerable. It is worth noting, however, that at present, even some newer medications are prescribed with pegylated interferon and/or ribavirin depending on past treatment experience, liver damage, or response-guided therapy. The persistence of out-dated therapies is itself impactful, as one support worker commented, *"For those who do get the treatment, dealing with the side-effects can be extremely difficult, in particular, the depression. The injections associated with the interferon can also be a triggering factor for many people as well as a source of anxiety, given that many individuals being treated for hepatitis C have a history of injection drug use."* This was echoed by many caregivers, who regularly noted the social impacts of HCV treatment, including *"heavy pill burden, multiple side effects, dealing with needle phobia, or triggers with regard to past lifestyle."*

Respondents identify the most persistent treatment side effects of any HCV treatment as being, *"fatigue Insomnia Constant (daily) headaches Weight loss Suppressed appetite Hair loss Some cognitive difficulties such as word recall Depression Irritability & easy to anger Short term memory loss Joint pain."* Fortunately, the treatment landscape continues its robust and dynamic course and patient groups are extremely optimistic about the safety and efficacy of new DAAs while being very concerned about the public availability and accessibility of the same.

CTAC enjoys the participation of many patients experienced with first generation *and* some experienced with newer and current-generation HCV therapies, and all respondents have expressed a positive outlook regarding the trials our webinars have discussed. Specifically in the reports of few serious adverse events, minimal drug-drug interactions, and a comprehensive safety profile. Further, many respondents chose to contextualize this development as indicative

of an industry-wide pharmaceutical response to the community call for more tolerable cures for HCV.

As a result of reviewing clinical trial data and engaging with the treatment experiences of our members living with hepatitis C, CTAC has identified six key unmet needs in hepatitis C treatment, many of which are reflected in the quotations above, provided by respondents. They are:
-Increased successful treatment outcomes (SVR)
-Shortened treatment
-Minimized adverse events
-Interferon-free treatment
-A functional hepatitis C cure for all patients (across genotypes, levels of liver damage and responses to previous treatments)

2.4 Impact on Caregivers

As one caretaker respondent reported, *"Living with someone who is taking interferon & ribavirin can be extremely challenging."* Another respondent, themselves treatment-experienced, noted the impact treatment had not only on their well-being, but their relationships, noting that *"Interferon is a very taxing, difficult drug. We need to eliminate it as soon as possible… I suffered through virtually a whole year of treatment on the interferon regimen and it was brutal."* Later generation therapies involving DAAs such as boceprevir and telaprevir, increased SVR and often reduced treatment durations. However, as per the ADVANCE and SPRINT-2 studies, as well as the 2012 black-box warning regarding telaprevir's association with adverse dermatological events and boceprevir's association with severe anemia, the HCV community became more vocal in their demand for well-tolerated treatment.
Because hepatitis C treatment is extremely arduous, causing people to feel chronic fatigue, mental health side effects and other serious adverse events for a period of several weeks, caregivers' lives are also affected by the current standard of care. The caregivers who participated in the survey noted the following challenges associated with the current standard of care facing the people living with hepatitis C they support: adherence, multiple side effects/adverse events including fatigue, nausea, depression, adequate nutrition and food security, anorexia/weight loss, as well as treatment failure (and anxiety anticipating potential treatment failure).

Caregivers who responded to the survey found it difficult to provide support to people undergoing hepatitis C treatment, especially in ways the social safety net is inadequate to meet the needs of people living with hepatitis C. One caregiver respondent to a previous survey stated, "*Treatment is difficult for those who have their social determinants of health met. It is almost impossible for those who don't.*"

One respondent to a previous survey who had undergone hepatitis C treatment reported feeling like a burden to her/his family. The respondent noted: "*I was somewhat of a burden to my spouse during treatment as there were many regular activities I simply didn't have the energy to perform – household chores, repairs etc. and was often not up to socializing with other people.*" This relationship stress can certainly be mitigated by new medications that reduce treatment duration and minimize side effects.

Further, caregivers expressed concern in their capacity to stay informed on new treatment developments or the availability of certain drugs in some provinces but not others. The ability to help their patients navigate the health care landscape and significant virology learning required

to consistently understand HCV treatments were identified as skills caregivers found little support in developing, but which were extremely important in their work.

Section 3 — Information about New Drugs

3.1 Information Gathering

The information in this section was gathered in the same means described in section 2.1.

3.2 What Are the Expectations for New Drugs or What Experiences Have Patients Had to Date With New Drugs?

Many of our respondents were experienced with some DAA therapy.

Direct-Acting Antivirals are a dynamic and exciting new treatment class that is significantly improving the health outcomes of people living HCV. Increasingly successful SVR rates and more tolerable rates of adverse events and/or side effects are changing many patients attitudes toward treatment. In consultation with membership and patient respondents, CTAC expects that DAAs will improve and enhance patients lives in the following ways:

-Increased Successful Treatment Outcomes (as measured by SVR): new DAAs are routinely boasting SVR24 numbers of >95%. Many new trials are seeing >90% in SVR12 studies. Most present-day studies are also checking and evaluating SVR at 4 weeks, and seeing >70% rates (Hallmark-Dual, Ally, Unity; daclatasvir and asunaprevir). No study is stopping at 4 weeks, but the point remains that DAAs are becoming more and more effective with shorter treatment regimens.
-Shortened Treatment: sofosbuvir set the 12 week SVR standard for new DAAs and now many such medications are able to consistently meet that mark for more than 90% of patients. Shortened treatment increases adherence, reduces adverse events, and eases the course of treatment for the patient.
-Safer, More Tolerable Treatment: new DAAs are more tolerable and appear to illicit fewer adverse events in clinical trial settings. As sofosbuvir and simeprevir replaced boceprevir and telaprevir, we expect DAAs to continue to evolve to become more safe and tolerable while still increasing efficacy. Apprehension and anxiety concerning side effects is still a major issue in deterring people from receiving treatment.
-Interferon-Free, Ribavirin-Free Treatment: while we understand that ribavirin still demonstrates efficacy in some population subsets, in some patient profiles, and in some genotypes, patient consultations have concluded that industry must continue to develop treatment away from both interferon and ribavirin. Much clinical trial data suggests that for G1A patients, we can eliminate interferon entirely as well as either eliminate or significantly reduce the use of ribavirin.

Section 4 — Additional Information

CTAC would like to thank CADTH for the opportunity to respond to this therapeutic review. CTAC would like to reiterate its endorsement for the continued use, development, and provincial-formulary-listing of new, effective, and tolerable DAAs as they are developed.

In many cases, new DAAs are being used in combination or co-formulation with other DAAs, and in fact, clinical trial data is evaluating many varied combinations. We hope that CDEC will not limit DAA use based on combinations already listed or studied in Ph. III clinical trials. We recommend that new DAAs be suggested for use with agents under the supervision of a physician familiar with current HCV evidence and trial data. Consider that asunaprevir and daclatasvir were submitted independently to the CDR, but are more often found as components in other combinations. Patient input is directed to evaluate these components separately, but

CTAC acknowledges that most clinical trial data evaluated them in their combinations. Clinical trials are presently pairing, co-formulating, and measuring many DAAs together or against one another. This is part of the contemporary dynamism and velocity with which the HCV pipeline is presently moving. We trust that CDEC will bear this in mind in addressing the speed with which medications can be reviewed and how they are recommended for listing.