

# The revolutionary changes in hepatitis C treatment: A concise review

The replacement of interferon-based therapy with highly effective and well-tolerated direct-acting antiviral therapy makes eliminating hepatitis C infections in British Columbia a realistic goal.

**ABSTRACT:** Since hepatitis C was discovered in 1989, the pharmacological management of infections caused by the virus has undergone revolutionary changes, significantly improving cure rates and reducing patient morbidity and mortality. Early treatment options included interferon and ribavirin, which were associated with significant side effects and poor efficacy. In 2011 the first direct-acting antiviral agents were introduced and since have continued to improve both the efficacy and tolerability of treatment. The development of the direct-acting antiviral agents has reduced disease burden, expanded treatment options for patients with different hepatitis C genotypes or other pre-existing

comorbidities, and significantly improved cure rates, which now exceed 95% with newer antiviral agents. Barriers to using this therapy in British Columbia include suboptimal population screening and diagnosis, variable patient and physician knowledge, high drug costs, lack of insurance coverage for some antivirals, and difficulty accessing coverage under Pharmacare. Reinfection is also an ever-present risk. Using the antiviral therapies currently available and ensuring patients have better access to care would make eliminating hepatitis C possible in British Columbia, especially if health care providers, patient communities, and government agencies all strive to achieve this goal.

**W**orldwide, hepatitis C is a major public health concern, with an estimated 71 million people being chronically infected with the virus ([www.who.int/news-room/fact-sheets/detail/hepatitis-c](http://www.who.int/news-room/fact-sheets/detail/hepatitis-c)). Individuals with untreated hepatitis C infection have an approximate fivefold increase in all-cause mortality and a twentyfold increase in liver-related mortality.<sup>1</sup> Acute hepatitis C infections can present asymptotically, and approximately 85% of acute infections will develop into chronic disease.<sup>2</sup> Chronic hepatitis C infections can cause significant liver damage, including the development of cirrhosis and hepatocellular carcinoma.<sup>3,4</sup> In addition

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to the hepatic manifestations, acute and chronic hepatitis C can have extra-hepatic manifestations, including disease processes associated with the virus and more specific immune-related end-organ effects.<sup>5</sup> Disease processes associated with hepatitis C infection include renal insufficiency, type 2 diabetes, and insulin resistance, while more specific hepatitis C immune-related manifestations include sicca syndrome, arthralgia, myalgia, and mixed cryoglobulinemia.<sup>5</sup> The hepatic and extra-hepatic manifestations contribute to the huge burden of disease that negatively impacts patient well-being and quality of life.

In British Columbia, more newly reported hepatitis C cases are reported than elsewhere in Canada,<sup>1</sup> with the Metro Vancouver area having an alarmingly high incidence rate of 37.3 per 100 person-years among young injection drug users.<sup>6</sup> In a recent study of more than 1.1 million individuals in BC tested for hepatitis C, a prevalence rate of 5.8% was reported.<sup>1</sup> While high incidence rates are associated with sex-trade work, incarceration, and injection drug use, high prevalence rates in British Columbia are associated with the following: male gender, a birthdate from 1945 to 1964, HIV or hepatitis B coinfection, a mental health condition, a substance and/or alcohol abuse disorder, and low socioeconomic status.<sup>1</sup>

Despite advances in management and better understanding of viral genotypes,<sup>7</sup> hepatitis C infection continues to pose a threat to public health in Canada and other countries.<sup>2</sup>

## Screening

A high proportion of Canadians with chronic hepatitis C infection remain undiagnosed,<sup>8</sup> making it important for physicians and other health care providers to understand screening recommendations that will help with

diagnosis and, ultimately, eradication of hepatitis C. The Canadian Association for the Study of the Liver released updated guidelines in 2018 that include recommendations on the assessment, evaluation, and management of hepatitis C.<sup>8</sup> The 2018 guidelines recommend taking a risk-based and population-based approach to screening.<sup>8</sup> Chronic hepatitis C infection is prevalent in individuals born from 1945 to 1975.<sup>8</sup> Despite the high prevalence of hepatitis C infection in this birth cohort, screening rates are low<sup>8</sup> and the guidelines recommend one-time screening in all individuals in the 1945 to 1975 birth cohort, independent of individual risk factors.<sup>8</sup> For those with risk factors, testing for hepatitis C infection is recommended.

Some notable risk factors for hepatitis C are:

- A history of injection drug use.
- Having received a blood transfusion, blood products, or an organ transplant in Canada before 1992.
- A history of or current incarceration.
- Having received chronic hemodialysis.
- HIV infection.

Initial screening includes a test for hepatitis C antibodies.<sup>8</sup> If test results are positive, active infection should be confirmed with an RNA screen for hepatitis C.<sup>8</sup> Subsequently, patients should be referred to practitioners with experience in hepatitis C management to optimize treatment and outcomes.<sup>8</sup>

The 2018 guidelines also recommend that patients with confirmed hepatitis C infections undergo further testing to help establish a baseline and individualize treatment.<sup>8</sup> Suggested testing includes routine blood work with a complete blood count, liver enzymes (alanine transaminase, aspartate transaminase, alkaline phosphatase), liver function (bilirubin, INR, albumin), and creatinine.<sup>8</sup> Addi-

tionally, serology is recommended to exclude other infections (HIV, hepatitis B) and common liver diseases (transferrin saturation for hemochromatosis evaluation, IgG for autoimmune hepatitis).<sup>8</sup> Furthermore, all patients with hepatitis C should undergo staging of their liver disease, including a baseline ultrasound and evaluation for fibrosis.<sup>8</sup>

Other recommendations include resistance testing, if indicated, and genotype testing.<sup>8</sup> Six hepatitis C genotypes have been identified based on nucleotide differences. In turn, these numbered genotypes have been further classified by letter (1a, 2b, 3c, etc.).<sup>7</sup> Geographic differences are seen in the prevalence of some variants, with genotypes 1, 2, and 3 being common throughout the world, genotype 4 being common in the Middle East, and genotype 1 being overwhelmingly dominant in North America. Knowing a patient's genotype can help select the most effective treatment.

## Early treatment options

The first pharmacological regimen for hepatitis C was introduced in the 1990s and consisted of non-pegylated interferon alpha-2a or alpha-2b monotherapy.<sup>9</sup> The treatment duration was 24 or 48 weeks, depending on the hepatitis C genotype, and required thrice weekly injections.<sup>9</sup> As well as being cumbersome to patients and having significant side effects, the treatment was not very successful in achieving viral clearance as measured by the sustained virological response—undetectable hepatitis C RNA levels at 12 weeks or 24 weeks following the end of therapy. To increase the rates of sustained virological response, ribavirin was added to the interferon alpha treatment regimen, which improved outcomes and increased the response rates to approximately 30% to 40%.<sup>9</sup> However, treatment

response was heavily dependent on the hepatitis C genotype, with relatively poor cure rates reported in cases of genotype 1 and 4.<sup>9</sup>

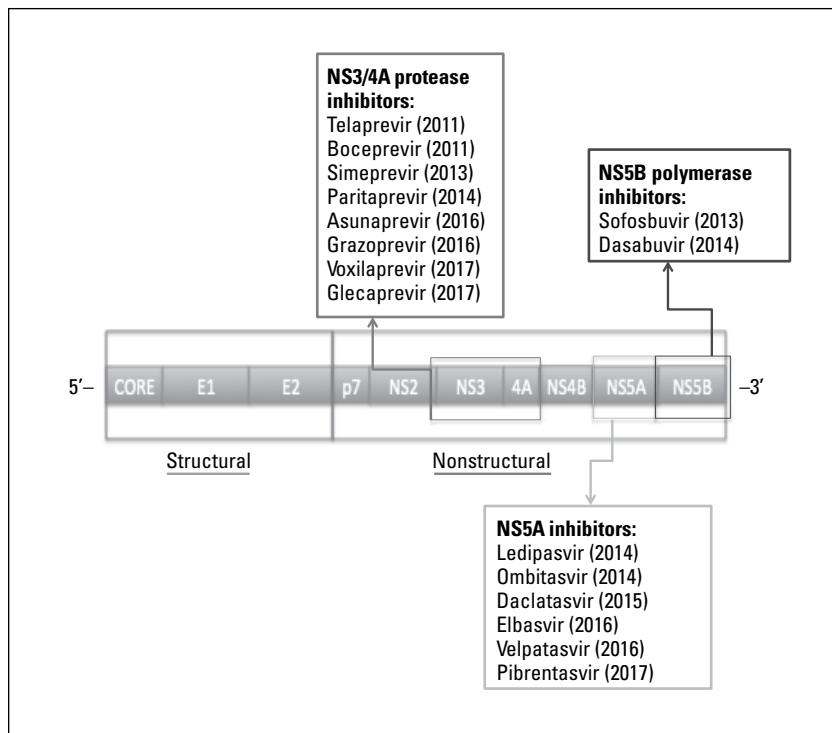
In the latter half of the 1990s, pegylated interferon alpha formulations were introduced. Pegylation slows down the rate of drug absorption, reduces distribution, and decreases the rate of elimination.<sup>10</sup> With pegylation, ideal plasma concentrations for inhibiting viral replication are better maintained, improving drug efficacy and increasing rates of sustained virological response.<sup>10</sup> However, response rates for pegylated interferon were found to be heavily dependent on patient-specific characteristics: body mass index, degree of pretreatment hepatic damage (specifically, cirrhosis), IL-28B genotype, and hepatitis C RNA viral load. In

cases of patients with treatment experience, the response to previous treatment (i.e., relapse vs nonresponse) was also a factor.<sup>11,12</sup> Although patients treated with pegylated interferon plus ribavirin required only one rather than multiple injections per week, the therapy had a number of side effects.<sup>10</sup> Adverse effects associated with interferon therapy included neutropenia, thrombocytopenia, alopecia, hypothyroidism, hyperthyroidism, flu-like symptoms, nausea, vomiting, and weight loss.<sup>13</sup> Interferon therapy was also associated with neuropsychiatric side effects, namely impaired memory and concentration, depression, and irritability.<sup>13</sup> Additional side effects associated with ribavirin specifically included anemia, respiratory complications, and teratogenicity.<sup>13</sup> Due to the many po-

tential systemic toxicities and complications, interferon therapy was contraindicated in many patients. For genotype 1, the most common genotype in Canada, the likelihood of achieving a sustained virological response was a disappointing 40%, at best, in noncirrhotic patients after 48 weeks of therapy.<sup>14</sup> For the combined genotype 2 and 3 patients, 24 weeks of pegylated interferon and ribavirin yielded a sustained virological response of 76%.<sup>15</sup> Cirrhotic patients in general responded less well to any interferon-based therapy, and those with advanced cirrhosis requiring a liver transplant tolerated the therapy poorly and experienced significant adverse side effects, including worsening decompensation and death.<sup>16</sup> In short, interferon-based therapies were associated with significant side effects and suboptimal treatment success rates, and the use of interferon was contraindicated in patients with advanced liver disease.

### Current treatment options

In 2011 the first direct-acting antiviral agents were developed and approved for the treatment of hepatitis C infection.<sup>17</sup> These novel antiviral medications include the following classes of drugs: NS3/4A protease inhibitors, NS5A replication complex inhibitors, and NS5B polymerase inhibitors. As shown in the **Figure**,<sup>18</sup> direct-acting antiviral agents were developed to target the products of the nonstructural coding sequence of hepatitis C, thus directly impairing the replicative machinery of the virus rather than relying on the nonspecific antiviral effects of pegylated interferon and ribavirin.<sup>7</sup> The **Table** shows a list of the currently available products and their pivotal registration clinical trials.<sup>19-53</sup> Each product uses a combination of drugs to achieve an additive or synergistic effect. The cure rates with these



**Figure.** Direct-acting antiviral agents used to target products of the nonstructural coding sequence of hepatitis C. The year each agent received FDA approval is indicated in brackets.<sup>6,18</sup>

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extremely well tolerated antiviral formulations is 95% to 99%.

### Barriers to overcome

Treatment of hepatitis C has undergone revolutionary changes since the early 1990s. The introduction of direct-acting antivirals in particular has improved cure rates and reduced patient all-cause and liver-specific mortality and morbidity. Treatment has gone from being cumbersome and

ineffective to being well tolerated and highly effective. But although good treatment options exist, the complete eradication of the disease in British Columbia will require overcoming some barriers. These include suboptimal population screening and diagnosis, variable patient and physician knowledge, high drug costs, lack of insurance coverage for some antivirals, and difficulty accessing coverage under Pharmacare. In addition,

direct-acting antivirals do not work for a small but real minority, and reinfection is an ever-present risk.<sup>54</sup>

The World Health Organization has declared that eliminating hepatitis C globally by 2030 is feasible.<sup>55</sup> Using the antiviral therapies currently available and ensuring patients have better access to care would make eliminating hepatitis C a realistic goal in British Columbia, especially if health care providers, patient communities,

**Table. Commonly used direct-acting antiviral agents in Canada.**

Brand name	Manufacturer	Geno-type	Drugs and doses	Treatment duration	Common side effects	Notable drug-drug interactions	Important drug trials	BC Pharma-care coverage	Additional Comments
Harvoni	Gilead Sciences <sup>19</sup>	1a, 1b, 4, 5, 6 <sup>8</sup>	90 mg ledipasvir, 400 mg sofosbuvir <sup>19,20</sup>	8–24 weeks <sup>8</sup>	Fatigue, nausea, headache, diarrhea, insomnia <sup>19</sup>	Amiodarone, P-glycoprotein inducers (e.g., rifampin, St. John's wort) <sup>20</sup>	ION I, ION II, ION III, SYNERGY, SOLAR-I, ION-IV, ELECTRON-2 <sup>21–26</sup>	Yes	
Epclusa	Gilead Sciences <sup>27</sup>	1–6 <sup>8</sup>	400 mg sofosbuvir, 100 mg velpatasvir <sup>27</sup>	12 weeks <sup>8</sup>	Headache, fatigue <sup>27</sup>	Amiodarone, proton-pump inhibitors, digoxin, rosuvastatin, tenofovir, P-glycoprotein inducers <sup>27</sup>	ASTRAL 1, ASTRAL 2, ASTRAL 3, ASTRAL 4, ASTRAL 5 <sup>27–31</sup>	Yes	
Zepatier	Merck <sup>32</sup>	1a, 1b, 4 <sup>8</sup>	50 mg elbasvir, 100 mg grazoprevir <sup>32</sup>	12–16 weeks <sup>8</sup>	Fatigue, nausea, headache <sup>33</sup>	CYP3A inducers (e.g., efavirenz), CYP3A inhibitors (e.g., lopinavir) <sup>33</sup>	C-EDGE TN, C-EDGE TE, C-SWIFT, C-WORTHY, C-EDGE, C-SURFER, C-EDGE CO-STAR <sup>33–39</sup>	Yes	For use in patients with chronic kidney disease (including dialysis patients) <sup>39</sup>
Vosevi	Gilead Sciences <sup>41</sup>	1–6 <sup>8</sup>	400 mg sofosbuvir, 100 mg velpatasvir, 100 mg voxilaprevir <sup>41,42</sup>	12 weeks <sup>8</sup>	Headache, fatigue, nausea, diarrhea <sup>41</sup>	Amiodarone, CYP inducers, P-glycoprotein inducers, strong inducers of OATP1B1/B3 (e.g., rifampin) <sup>41</sup>	POLARIS 1, POLARIS 2, POLARIS 3, POLARIS 4 <sup>43,44</sup>	Yes	
Maviret	AbbVie <sup>45</sup>	1–6 <sup>8</sup>	100 mg glecaprevir, 40 mg pibrentasvir <sup>45</sup>	8–16 weeks <sup>8</sup>	Headache, fatigue <sup>46</sup>	Amiodarone, HMG CoA reductase inhibitors, carbamazepine, efavirenz, proton-pump inhibitors <sup>46</sup>	SURVEYOR-I, SURVEYOR-II, ENDURANCE-I, ENDURANCE-II, ENDURANCE-III, EXPEDITION-I, EXPEDITION-II, EXPEDITION IV, MAGELLAN-I, MAGELLAN-II <sup>47–52</sup>	No	For use in patients with chronic kidney disease (including dialysis patients) <sup>53</sup>

and government agencies all strive to achieve this goal. **BCMJ**

### Competing interests

Over the past 22 years Dr Yoshida has been an investigator in hepatitis C clinical trials sponsored by Gilead Sciences, Merck (previously Schering-Plough), Janssen, AbbVie, Vertex, Hoffmann-La-Roche, Boehringer Ingelheim, Pfizer, Human Genome Sciences, and Novartis. In the past 2 years he has received honoraria for CME/Ad Board lectures from Gilead Sciences Canada, Merck Canada, and AbbVie Canada.

## Treatment of hepatitis C has undergone revolutionary changes since the early 1990s.

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