This is the 1st Affidavit
of Dr. Vince Bain in this case
and was made on 11/Mar/2015

No. No. C965349
Vancouver Registry

In the Supreme Court of British Columbia

Between

Anita Endean, as representative plaintiff

Plaintiff

and

**The Canadian Red Cross Society
Her Majesty the Queen in Right of the Province of British Columbia, and The Attorney General of Canada**

Defendants

and

Prince George Regional Hospital, Dr. William Galliford, Dr. Robert Hart Dykes, Dr. Peter Houghton, Dr. John Doe, Her Majesty the Queen in Right of Canada, and Her Majesty the Queen in Right of the Province of British Columbia

Third Parties

Proceeding under the *Class Proceedings Act*, R.S.B.C. 1996, C. 50

AFFIDAVIT

I, DR. VINCE BAIN, of University of Alberta, 1.55 Zeidler Center, 130 University Campus, Edmonton, Alberta, SWEAR (OR AFFIRM) THAT:

Qualifications

1. I am a physician specializing in gastroenterology and hepatology. I am a Fellow of the Royal College of Physicians of Canada in Internal Medicine and in Gastroenterology. I am a member of the College of Physicians and Surgeons in Alberta. I am Board certified by the American Board of Internal Medicine.

2. I have a clinical practice as well as teaching responsibilities at the University of Alberta. In my clinical practice, I treat persons who are infected with the Hepatitis C Virus ("HCV"). I estimate that I currently treat or follow 200 HCV patients. I estimate that I have treated more than 500 HCV patients over the course of my career.

3. I am a Professor in the Division of Gastroenterology, Department of Medicine at the University of Alberta I have had this position since 2002. I am also the Medical Director of the Liver Transplant Program at the University of Alberta and have been since 1989. Since 2000 I have been the Director of the Liver Unit, Division of Gastroenterology, Department of Medicine, at the University of Alberta.

4. From 2000-2002 I was the Chairman of the Hepatology and Liver Transplant Committee of the Canadian Association of Gastroenterology. I am a member of the Canadian Association for the Study of the Liver, known as CASL, a society consisting of Canadian gastroenterologists and hepatologists (gastroenterologists who specialize in the treatment of the liver). From 2002-2004 I was the President of CASL. From 2004-2006 I was the Chairman of the Medical Advisory Board of the Canadian Liver Foundation.

5. A copy of my curriculum vitae is attached as **Exhibit "A"** to this affidavit.

6. This affidavit addresses the nature of HCV, its disease stages, co-morbidities, treatment, and outcomes. I have reviewed the affidavits of Dr. Frank Anderson sworn in this matter. This affidavit updates the information provided in those affidavits, particularly in the area pertaining to treatment and treatment outcomes. The sections of this affidavit headed the Hepatitis C Virus and Course of Infection include summaries of the more detailed information provided in Dr. Anderson's previous affidavits to provide the reader with context to understand the updates on treatment and outcomes. Those previous sections are summarized (as opposed to composed anew) as I agree with them and saw no need to rewrite them.

7. In making this affidavit, I certify that I am aware that my duty is to:

(a) provide opinion evidence that is fair, objective and non-partisan and related only to matters within my area of expertise; and

(b) assist the court and provide such additional assistance as the court may reasonably require to determine a matter in issue.

8. I am aware that the foregoing duties prevail over any obligation I may owe to any party on whose behalf I am engaged and I am aware that I am not to be an advocate for any party. I confirm that this affidavit conforms with the above-noted duties. I further confirm that if called upon to give oral or written testimony, I will give such testimony in conformity with these duties.

The Hepatitis C Virus

9. Hepatitis means inflammation of the liver. Inflammation causes damage to liver cells and death of liver cells. Ongoing inflammation leads to fibrosis which is progressive. The virus causing Hepatitis C was identified in late 1989 and the first diagnostic serum tests appeared in 1990.

Nature of the Virus and Genotypes

10. HCV is a ribonucleic ("RNA") virus. The virus takes the form of six different "genotypes" which vary in distribution worldwide. These genotypes are described with numbers 1 to 6. There are smaller differences within each genotype referred to as "subtypes", and these are designated a, b and c. The process of determining the genotype and subtype with which a person is infected is called genotyping and subtyping.

11. Some patients may have a more virulent clinical course, and certain genotypes respond less well to a given treatment than others. The virus may mutate during viral replication and possibly as a result of treatment. This is common in RNA viruses because their method of replication involves many spontaneous errors. Mutation, particularly during treatment, may cause the virus to become resistant to treatment.

12. It is standard to conduct a genotype assessment of all persons undergoing treatment and to tailor the treatment based on the genotype.

13. The various genotypes in Canada are as follows:

(a) genotype 1 accounts for approximately 65% of Canadians infected with HCV (this number varies from province to province);

(b) genotype 2 accounts for approximately 14% of Canadians infected with HCV;

(c) genotype 3 accounts for approximately 20% of Canadians infected with HCV; and

(d) a very small proportion of Canadians infected with HCV are infected with genotypes 4, 5 and 6 (less than 1 %).

Blood Tests for Diagnosis

14. Blood tests are used to determine whether a person is or was infected with HCV. The presence of the antibody to HCV in the blood of a person reveals whether or not the person has ever been infected with HCV. It does not determine whether the person is currently infected with HCV or when the person became infected with HCV. A polymerase chain reaction ("PCR") test reveals whether detectable levels of RNA of the virus are present in the blood of a person, and as such determines whether a person is currently infected with HCV.

Course of Infection

Acute HCV

15. Once infected with HCV, a person will either clear HCV after an acute stage of the illness within approximately six months of infection, or the person will develop chronic HCV infection. The medical literature establishes that approximately 25% of all persons infected clear HCV within approximately one year of infection. Those persons

will still test positive for the antibody but will not test positive on a PCR test, nor will they experience any progressive liver disease due to HCV.

Chronic HCV – Inflammation and Fibrosis

16. Persons who do not clear the virus after the acute stage of the illness have chronic HCV. The extent to which they experience progressive liver disease depends on the virulence of their particular virus and host factors such as their age, their alcohol intake and whether treatment achieves a sustained viral response which is synonymous with cure (described below).

17. HCV causes inflammation, scarring (fibrosis) and death (necrosis) of liver cells.

18. The level of inflammation varies among HCV patients. The various levels of inflammation are referred to as grades and the grading system is from 0 to 4 in the Metavir system. Zero inflammation means no inflammatory cells, and grade 4 inflammation means severe inflammation throughout the whole of the liver lobule. The higher the grade of inflammation, the more inflammatory activity is present. The inflammation may vary in intensity from time to time, at times being much more severe than other times.

19. Inflammation and necrosis of liver cells results in scarring of liver tissue (fibrosis). Fibrosis also appears in various patterns in HCV patients, and these patterns are referred to as stages. The higher the stage, the more marked the pattern of fibrosis in the liver.

20. Fibrosis generally increases over time. Research has been done on the development of fibrosis, and indicates that the process of fibrosis and scar formation is fairly lengthy. There is a stage at which fibrosis is "immature" i.e. the scar formation has not condensed, and such immature fibrosis may improve with sustained viral response after therapy.

21. The stages of fibrosis are based on the predictable pattern of scarring which hepatitis causes in the liver. The liver consists of anatomic units referred to as liver

lobules. Each liver lobule has a central vein and portal triads which are joined by lines or tracks of liver cells. Blood enters the liver through arteries and veins in the portal triads, flushes along the liver cells, and leaves through the central vein.

22. In chronic viral hepatitis the inflammation is more prevalent in and around the portal triads. The cells around the portal triads may be destroyed (cell necrosis), a process referred to as interface hepatitis. The inflammation progresses beyond the portal triads along the liver tracks to reach the central veins. Fibrosis confined to the portal areas or with short extensions is referred to as non-bridging fibrosis (F1 or F2). When the pattern of fibrosis begins to extend from a portal triad to a central vein, or between portal triads, the fibrosis is referred to as bridging (F3). Bridging between all the veins and all the triads and between all the triads in a lobule is called cirrhosis. This pattern is characterized by complete circles of scar or fibrosis as viewed in two dimensions as we see on liver biopsies (or spheres in 3D) and this causes the typical nodular pattern of a cirrhotic liver (F4).

23. The most commonly utilized method (Metavir) of staging fibrosis utilizes the following four stages:

(a) F0 – no fibrosis (disease levels 1 and 2 in the Settlement Agreement and Plans);

(b) F1 – minimal fibrotic changes which do not extend beyond the portal areas (included in disease level 3 in the Settlement Agreement Plans);

(c) -F2 – fibrotic changes to portal areas with short extensions (included in Disease Level 3 in the Settlement Agreement Plans);

(d) F3 – fibrotic changes to the liver known as bridging fibrosis (corresponds to Disease Level 4 the Settlement Agreement Plans); and

(e) F4 – cirrhosis – fibrotic changes which have become cirrhotic (corresponds to Disease Level 5 in the Settlement Agreement Plans).

24. Many patients are asymptomatic prior to developing cirrhosis or HCC.

25. Pre-cirrhotic symptoms, for those who experience them, include: fatigue, weight loss, upper right abdominal discomfort, mood disturbance, poor concentration, anxiety and depression. Of those symptoms, fatigue is the most common. Patients typically describe the fatigue as a feeling of exhaustion and lack of energy.

Cirrhosis and End Stage Liver Disease

26. Once a patient is cirrhotic, they are either a compensated cirrhotic, or a decompensated cirrhotic, depending on their liver function. Where there are enough viable liver cells to maintain liver function, notwithstanding the cirrhotic pattern, the person has compensated cirrhosis.

27. Decompensated cirrhosis occurs when the liver is no longer able to perform one or more of its essential functions. It is caused by loss of liver cells, but more importantly, by progressive fibrosis that interferes with normal blood flow through the liver. It is diagnosed by the presence of one or more conditions which alone or in combination is life threatening without a transplant. This is also referred to as liver failure or end stage liver disease.

28. With decompensated cirrhosis critical liver functions are impaired and the condition is referred to as liver failure. Life is threatened. Conditions which define liver failure include gastrointestinal haemorrhaging, ascites (fluid build up in the abdomen), inadequate excretion of bilirubin by the liver causing jaundice or failure to remove the usual toxins absorbed from the bowel (which in turn can affect brain cells causing drowsiness, confusion and possibly coma, known as hepatic encephalopathy). These severely ill patients also experience protein malnutrition causing bruising, bleeding and muscle wasting. Other organ failure may occur with progressive disease most commonly involving the lungs and kidneys.

29. Patients who progress to cirrhosis with or without decompensation may develop hepatocellular cancer ("HCC"). This is a primary form of liver cancer secondary to viral infection or cirrhosis. HCC is included in Level 6 in the Settlement Agreement Plans.

Co-Morbidities

30. Some patients with HCV suffer from conditions which are related to their infection with HCV; others to which they are more vulnerable to developing as a result of infection with HCV; or others for which HCV exacerbates the condition. Some of these are conditions which also occur in patients who do not have HCV. Such conditions are considered co-morbidities and they include:

(a) HCC - discussed above;

(b) pain – in general liver disease is not painful but some patients experience upper right quadrant pain and HCV-associated fatigue can exacerbate other medical conditions which have pain;

(c) mental illnesses such as depression and anxiety – HCV patients, some of whom have a history of intravenous drug use ("IVDU"), often have mental illnesses. HCV patients who have no history of IVDU also can experience mental illness but it is less frequent. It is understood that HCV affects the brain in some ways, and some patients describe "brain fog" and have difficulty concentrating. Other HCV patients have a reactive depression, ie: reactive to liver disease with a chronic course and a potentially life-threatening outcome;

(d) diabetes – the incidence of diabetes is higher in the HCV population than the general population;

(e) mixed cryoglobulinemia – this refers to the production of abnormal proteins referred to as globulins. These proteins may form aggregates that can adversely effect small blood vessels sometimes causing inflammation in these vessels referred to as "vasculitis". Treatment of the HCV will reduce the severity of this condition but not completely cure it;

(f) erythema multiform, erythema nodosum, lichen planus and others - skin conditions that manifest as a rash over parts of the body or red raised bumps over the shins and lower legs;

(g) glomerulonephritis – inflammation in the kidneys due to vasculitis which results in protein and blood cells in the urine and in some instances results in kidney failure. Treatment of HCV, if successful, will reduce the severity of this disease and avoid kidney failure unless the patient has already progressed to kidney failure;

(h) thyroid diseases – both overactive (hyperthyroidism) and underactive (hypothyroid) thyroid disease may occur;

(i) polyarteritis – inflammation of small blood vessels with skin rash, arthritis and sometimes swelling of the legs;

(j) porphyria cutanea tarda – a condition characterized by painful blisters on the exposed skin areas, particularly the hands and face. The blisters break leaving open sores, which eventually heal but often leave a scar;

(k) thrombocytopenia – low platelets resulting in increased bruising and bleeding;

(l) uveitis, Mooren corneal ulcers – inflammation of the eye or ulcers of the cornea of the eye. These conditions may be serious and threaten eyesight;

(m) Sjogren's syndrome – lack of production of tears and saliva; and

(n) B-cell lymphoma – this is a cancer of the lymph glands, although the increased frequency in HCV is still debated.

Treatment

Antiviral Therapy

31. The Canadian Association for the Study of the Liver ("CASL") produces guidelines for the management of HCV every few years.

32. The most recent guidelines are the 2015 Consensus Guidelines from the Canadian Association for the Study of the Liver. They were published in the Canadian Journal of Gastroenterology and Hepatology, Can J Gastroenterol Hepatol Vol 29 No 1 January/February 2015. They are attached as **Exhibit "B"** to this affidavit. The CASL guidelines are recommendations rather than strict standards.

33. The goal of antiviral therapy is complete eradication of the virus from the patient, thereby stopping the inflammation and preventing further scarring and death of liver cells. Reversal of fibrosis is possible in some patients. In others with advanced cirrhosis the extent of scarring is so great that the liver may proceed to liver failure notwithstanding the cessation of inflammation. The precise threshold for recovery is not well understood and even in those patients who progress, eradication of the virus is still beneficial because if a liver transplant can be performed, the new liver will not be re-infected.

34. Eradication of the virus is determined by measuring the amount of virus in the blood on PCR testing. If the virus drops below detectable levels, and stays below detectable levels for 12 weeks after antiviral treatment, a sustained viral response ("SVR") has been achieved. This additional 12 weeks of observation is a surrogate way to show that the entire body and not just the blood compartment has been cleared of virus. If virus remains, for example in the liver or lymph nodes, despite the blood being clear at the end of treatment, it will begin to replicate and reappear in blood within 12 weeks.

35. The major forms of antiviral therapy in the history of treating hepatitis C have been as follows:

(a) interferon monotherapy which consisted of injections of interferon;

(b) combination interferon and ribavirin therapy, which progressed to delivery of the interferon in a long-acting, pegylated form, still injected, and ribavirin pills, known as pegylated interferon and ribavirin combination therapy; and

(c) direct-acting anti-viral agents, some of which were initially added to pegylated interferon and ribavirin combination therapy. Others are given without either interferon or ribavirin, some are given with one or the other of pegylated interferon or ribavirin, depending on the circumstances of the patient.

36. Both interferon and ribavirin can cause significant side effects. The number and adverse nature of the side effects are more pronounced with interferon. In addition, these drugs are contra-indicated for people with other medical conditions, co-morbidities or who are taking certain other drugs. Accordingly, there has been extensive research into direct-acting antiviral agents which are effective without interferon and/or ribavirin. Currently, antiviral therapy with direct-acting agents and without the use of interferon and/or ribavirin is possible for most persons infected with HCV, as described below.

37. The first generation of direct-acting antiviral agents were protease inhibitors called telaprevir and boceprevir and they were approved for treatment in 2011. They were prescribed with pegylated interferon and ribavirin. Although they had increased SVR rates compared to interferon and ribavirin alone, they also had severe side effects and many associated drug interactions. Telaprevir and boceprevir are rarely prescribed in Canada anymore.

38. The next direct-acting antiviral agent approved for use in Canada was simeprevir, which was also prescribed with pegylated interferon and ribavirin in genotype 1 patients. It was approved in 2013. Its use is now limited in favour of interferon-free combinations.

39. Also in 2013, sofosbuvir was approved for use with pegylated interferon and ribavirin for genotypes 1 and with ribavirin only for genotypes 2 and 3. Its use has also now changed, as described below.

40. In late 2014 and early 2015, treatments that exclude pegylated interferon and ribavirin were approved and they are the treatments that are and will be most commonly prescribed. They are:

(a) a combination of sofosbuvir and ledipasvir which was developed by Gilead and is marketed as Harvoni in Canada; and

(b) a combination of ombitsavir; dasabuvir; paritaprevir which is known in the HCV medical treating community as "3D" (for three direct-acting antiviral agents). This was developed by AbbVie, and is marked as the Holkira Pak. This combination also includes ritonavir as a "boost" in order to enhance the anti-viral effect by reducing metabolism of one of the active drugs. In some patients ribavirin will be necessary.

41. With a few exceptions described below, each of these advancements is effective in persons not previously treated; is effective in those treated previously who did not respond; has been associated with increased sustained viral responses among certain genotypes; has a shorter treatment duration, is available to an increased number of patients (fewer contraindications or incompatibilities); and is associated with increased chances of tolerating the treatment and being able to finish the course of treatment. In sum, the efficacy of treatment has increased from about 5-10% (interferon monotherapy) to 95-99% (direct-acting anti-viral agents), while decreasing the duration of treatment and increasing the number of persons who can be treated and complete treatment. Treatment challenges for certain categories of patients remain, such as genotype 3 patients with cirrhosis. In this group SVRs of about 80% can be achieved and improvements are expected.

42. The cost of treatment has also gone up. The range is about $50,000 for 8 weeks to $76,000 for 12 weeks. If ribavirin is added, the additional cost is approximately $3,800-$4,400 for 12 weeks.

Treatment Duration

43. Treatment duration is important for several reasons. Generally, the shorter the treatment the more likely it is that the drugs will be taken in the correct amount at the correct time, which increases the likelihood of a sustained viral response. In addition, if the drugs cause side effects or medical complications, the shorter the treatment the more likely it is that the patient can endure the treatment.

44. Treatment duration also affects affordability of the treatment. Some private health care plans and this Settlement Agreement cover the newest drugs. Provincial drug coverage plans consider new drugs as they are approved by Health Canada, but coverage, if it is provided, lags behind approval.

45. Under the older treatment regimes, treatment duration was response guided. Response guided therapy involves testing viral load at certain times during treatment and either discontinuing (because viral load has not decreased significantly) or continuing therapy.

46. With the current treatments of direct-acting anti viral agents, the CASL guidelines recommend treatment duration which is set at the outset and which depends on genotype, clinical stage of disease, whether the person has been previously treated and drug combination. These recommendations demonstrate variability in treatment length from 8 weeks to 24 weeks. The majority of patients will receive 12 weeks of treatment with either Harvoni or Holkira Pak. The following are the exceptions:

(a) genotype 1 patients who are not cirrhotic, have never been treated and who have a low viral count may be treated for 8 weeks with Harvoni;

(b) genotype 1 patients who are cirrhotic and who have failed treatment previously, will be treated with Harvoni for 24 weeks unless ribavirin is added, in which case they will be treated with Harvoni and ribavirin for 12 weeks. Ribavirin is less expensive than Harvoni so some will likely opt for a 12 week course of Harvoni and ribavirin in this patient subgroup;

(c) genotype 1a patients who have cirrhosis and who were treated previously but did not respond may be treated with the Holkira Pak for 24 weeks;

(d) genotype 2 patients who are cirrhotic will be treated for 12 weeks with pegylated interferon, sofosbuvir and ribavirin or with sofosbuvir and ribavirin for 16 weeks;

(e) genotype 3 patients. The treatment of genotype 3 patients is set out in Table 7 of the CASL guidelines. There are many options depending on the status of the patients. In summary, they will be treated for either 12 or 24 weeks and some will be treated with a combination of drugs including interferon and/or ribavirin if they can tolerate it.

Treatment of Persons Who Are Co-Infected with HIV

47. The guidelines for treatment of persons who are co-infected with HIV are published by the Canadian Institute of Health Research HIV Trials. The current guidelines, published in October 2014, are attached as **Exhibit "C"** to this affidavit.

48. The SVR rate in HIV co-infected persons under the treatments in use at this time, as described above, are very similar to those who are mono-infected. All HIV co-infected patients should be considered for treatment.

49. The guidelines were published before specific studies for HIV co-infection had been published on Harvoni or Holkira Pak and so those drugs are not included in the recommendations. In my view, Harvoni and Holkira Pak have surpassed the guidelines and will be the primary types of treatment for HIV co-infected persons.

Side Effects

50. Interferon and ribavirin both cause severe side effects that made the therapies contraindicated in patients with certain other health issues; that interfered with completion of the therapy due to complications which arose from the side effects; and that caused significant morbidity in many patients while on the therapy. The first

approved direct acting anti-viral agents, telaprevir and boceprevir, also had significant side effects that were severe in some patients.

51. Because Harvoni and Holkira Pak are effective in some patients without interferon or ribavirin, the side effects and contraindications of these new combinations are markedly diminished. These drugs cause side effects in some patients but they tend to be less severe, do not create contraindications for treatment and they are not expected to imperil the chances of the patient completing the treatment. The side effects noted in the studies leading up to their approval are:

(a) patients taking Harvoni experienced mild to moderate fatigue, headache, insomnia and nausea; and

(b) patients taking Holkira Pak experienced fatigue, headache, nausea, pruritus (itchiness), insomnia, diarrhea and asthenia (lack of energy).

Health Outcomes After A Sustained Viral Response

52. Many factors, including medical, psychological, age, and socio-economic, will play a role in determining whether a person returns to baseline health status after attaining an SVR. It must be remembered that many of the persons were infected with the disease for 10-30 years before being cured. The comparison of good health at the time they were infected to the time they were cured is not straightforward.

53. Persons who were not disabled from HCV prior to treatment and who obtain an SVR during treatment will not go on to develop disabling symptoms materially contributed to be HCV with these exceptions:

(a) as discussed above, achieving an SVR significantly reduces the risk of HCC but it is not reduced to zero. Persons who had HCV and attained an SVR still have a higher risk of HCC than the general population. HCC occurrence post-SVR would be considered to be materially contributed to by previous infection with HCV;

(b) persons who have been successfully treated and who are asymptomatic after treatment may have future symptoms if they have an additional liver insult such as infection with another hepatitis virus, an autoimmune disease or alcoholism. Their past infection with HCV would be considered to materially contribute to renewed symptoms after liver insult unless they had no scarring of the liver at the time of their cure; and

(c) persons who had advanced cirrhosis may have crossed a threshold whereby the damage to the liver is so profound that the liver will continue to progress towards decompensation.

54. Many persons who were pre-cirrhotic when treated but were disabled from working or performing household duties and services will recover post-SVR and be able to return to work and household duties within a year of cessation of treatment.

55. Fewer, but a still significant number of patients who have compensated cirrhosis when treated and who were disabled at the commencement of treatment return to work or household duties after SVR and do so within one year of the cessation of treatment. Patients with decompensated cirrhosis are rarely working when treatment commences. Generally, their ability to return to work will depend on whether they receive a liver transplant after achieving an SVR. If they do, many will return to work within a year of the liver transplant. In the absence of a liver transplant, those who have liver failure will not return to work even though an SVR is achieved.

56. Those who are not able to return to work or household duties are impacted by factors such as:

(a) continuation of the most common symptom of HCV – debilitating fatigue – which does not always improve post-SVR;

(b) co-morbidities which may be materially contributed to by their infection with HCV or may have no causal connection to infection with HCV;

(c) age;

(d) motivation which can be affected by the nature of the work or the ease of return to work; and

(e) the longer patients have been off work, the less likely they are to return.

57. After SVR, prior infection with HCV can be a material contributor to death in those who:

(a) had liver failure at the time SVR is achieved and liver transplant does not occur or is not successful;

(b) have a subsequent insult to the liver such as another hepatitis infection, an autoimmune disease, or alcoholism; or

(c) develop HCC.

Post-SVR Treatment and Monitoring

58. Persons who have cirrhosis prior to attaining an SVR require screening for HCC every six months. They may also need gastroscopies to screen for esophageal varices. They should be followed by a hepatologist, gastroenterologist or internal medicine specialist.

59. Persons who did not have cirrhosis do not usually need to continue to see a specialist but instead are treated by their family doctors. On follow up, if the liver function tests show an increase in their ALT, they should have a repeat HCV RNA test. Literature suggests recurrence of HCV in patients who achieve an SVR to be less than 2%.

Liver Transplants

60. Transplantation does not cure the infection, but restores healthy liver function. However, post-transplant, the rate of liver damage (fibrosis) is accelerated so that about 30% of patients, in the absence of treatment, will be cirrhotic by 5 years. Patients with recurrent HCV have a reduced lifespan over and above the reduced lifespan seen in liver transplant patients.

HCC

61. Treatment options for HCC include resection of the tumour, alcohol injection into the tumour, embolization of the blood supply to the tumour along with the injection of anticancer drugs or radioactive beads, and radiofrequency ablation of the tumour. Transplantation may be considered for selected tumours before there is much likelihood of metastasis (spread of the tumour outside of the liver).

SWORN (OR AFFIRMED) BEFORE ME)
at Edmonton, Alberta, Alberta, on)
11 /Mar/2015.)
)
)
)
)
A Notary Public or a Commissioner of)
Oaths in Alberta)

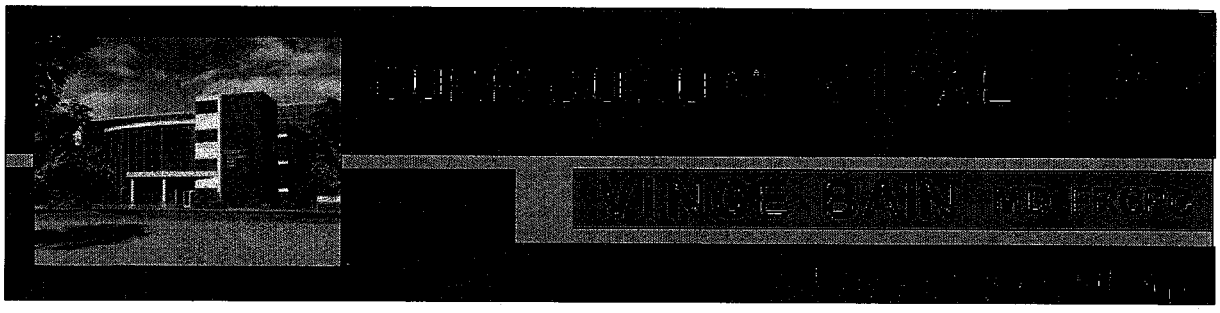
Yolanda Van Wachem
Barrister & Solicitor

DR. VINCE BAIN

This is Exhibit "A" referred to in the
Affidavit of DR. VINCE BAIN
sworn (or affirmed) before me at
Edmonton, Alberta,
this 11 day of MARCH 2015.

A Commissioner for the Province of ALBERTA

Yolanda Van Wachem
Barrister & Solicitor



November 3, 2014

BIRTHPLACE:	Edmonton, Alberta, Canada
CITIZENSHIP:	Canadian
DOB:	October 12, 1957
MARITAL STATUS:	Married - Lola T. Baydala (MD, FRCPC - Pediatrics) 3 Children (Graham, Jessie, Tamara)
EDUCATION:	1975 - Senior Matric (Honors) - Strathcona Composite High School, Edmonton. 1979 - B.Sc. with Distinction, University of Alberta, Edmonton, Canada. 1981 - M.D. First-Class Standing with Distinction, University of Alberta, Edmonton, Canada.
INTERNSHIP:	1981 - 1982 - Rotating Intern, Victoria Hospital, London, Ontario.
RESIDENCY:	1982 - 1985 - Resident in Internal Medicine, University of Alberta Hospital, Edmonton, Alberta. Director: Dr. A.M. Edwards.
FELLOWSHIPS:	1985 - 1987 - Gastroenterology, University of Alberta Hospital, Edmonton, Alberta. Director: Dr. A.B.R. Thomson. 1987 - 1989 - MRC Research Fellow, Liver Unit, Kings College Hospital, London, England. Supervisor: Dr. Roger Williams.
CURRENT POSITIONS:	Professor, Div of Gastroenterology, Dept of Medicine, University of Alberta, Edmonton, Canada, 2002 - present.

Medical Director, Liver Transplant Program,
University of Alberta, Edmonton, Canada, 1989-Present.

Director, Liver Unit, Div of Gastroenterology
Department of Medicine, University of Alberta
Edmonton, Canada, 2000 - Present

PREVIOUS POSITIONS:

Associate Professor, Div of Gastroenterology,
Dept of Medicine, University of Alberta,
Edmonton, Canada, 1995 - 2002

Assistant Professor, Division of Gastroenterology,
Department of Medicine, University of Alberta,
Edmonton, Canada, 1989 - 1994.

Program Director, GI Fellowship Program,
University of Alberta, Edmonton, Canada, 1992 - 1997.

NATIONAL ADMIN POSITIONS:

1998-2000	-Chairman, Education Comm, Cdn Assoc. for the Study of the Liver.
2000-2001	-Vice President, Cdn Assoc. for the Study of the Liver.
2000-2002	-Chairman, Hepatology and Liver Transplant Committee, Cdn Assoc. of Gastroenterology.
2002-2004	-Vice-Chair, Medical Advisory Board, Canadian Liver Foundation
2002-2004	-President, Cdn Assoc for the Study of the Liver.
2004 - 2006	-Chairman, Medical Advisory Board, Canadian Liver Foundation

PROFESSIONAL QUALIFICATIONS:

1981	- Licentiate, Medical Council of Canada.
1982	- National Board of Medical Examiners.
1985	- American Board of Internal Medicine.
1986	- Fellow of the Royal College of

		Physicians of Canada - Internal Medicine.
	1987	- Fellow of the Royal College of Physicians of Canada - Gastroenterology.
	1990	- Fellow, American College of Physicians.
LICENCES:	1983- Present	- College of Physicians and Surgeons of Alberta.

PROFESSIONAL SOCIETIES AND ORGANIZATIONS:

Alberta Medical Association.

American Association for the Study of Liver Disease.

Canadian Association of Gastroenterology.

Canadian Association for the Study of Liver Diseases.

Canadian Medical Association.

Canadian Transplant Society

European Association for the Study of Liver Diseases.

AWARDS

Jonathon B Meddings Clinical Innovation Award 2009-2010

Distinguished Service and Meritorious Achievement Award, Canadian Assoc for the Study of the Liver 2012

Excellence in Humanism Certificate, Presented by the Faculty of Medicine and Dentistry, 2013.

Awarded Fellowship Designation in the American Association For the Study of Liver Diseases, 2014.

JOURNAL AND GRANT REVIEWS:
(last 5 years)

2002 - 2012 - American Journal of Transplantation-Reviewer

2014 – Liver Transplantation – Reviewer

2014 – World Journal of Gastro - Reviewer

1990 - 2012 - Canadian Journal of Gastroenterology. **2000 - 2003**, Editorial Board

2009 - 2012 – Transplantation

2012 – Journal of Viral Hepatitis

2010 -2014– Hepatology – Reviewer

PUBLICATIONS:

A. Peer Reviewed Articles

1. Bain GO and **Bain VG**.
   Increased numbers of lymphocytes with single class surface immunoglobulins in Hodgkin's Disease.
   American Journal of Clinical Pathology 82:674, 1984.

2. **Bain VG** and Bain GO.
   Lymphocyte populations with abnormal Kappa: Lambda ratios in reactive lymphoid hyperplasia.
   Journal of Surgical Oncology 29:227, 1985.

3. **Bain VG**, Ardao GH, Kowalewska-Grochowska K, Wensel RH and Jewell LD.
   Biliary Ascariasis.
   Journal of Clinical Gastroenterology 10:448, 1988.

4. **Bain VG** and Alexander GJM.
   Progress in the treatment of chronic hepatitis B.
   Journal of Antimicrobial Chemotherapy 22:780, 1988.

5. **Bain VG**, Daniels HM, Chanas A, Alexander GJM, Williams R.
   Foscarnet therapy in chronic hepatitis B virus E antigen carriers.
   Journal of Medical Virology 29:152, 1989.

6. **Bain VG**, Bailey RJ, Jhamandas JH.
   Post-shunt myelopathy.
   Journal of Clinical Gastroenterology 13:562, 1991.

7. Lau JYN, Hansen LJ, **Bain VG**, Chaggar K, Smith HM, Portmann BC, Vergani D, Alexander GJM, Williams R.

Expression of intrahepatic hepatitis D viral antigen in chronic HDV infection.
Journal of Clinical Pathology 44:549, 1991.

8. Lau JYN, **Bain VG**, Davis SE, Alexander GJM, Williams R.
Export of intracellular hepatitis B virus (HBV) surface antigen in chronic HBV infection is related to viral replication.
Hepatology 14:416, 1991.

9. Lau JYN **Bain VG**, Naoumov NV, Smith HM, Alexander GJ Williams R.
Effect of gamma interferon on hepatitis B viral antigen expression in primary hepatocyte culture.
Hepatology 14:975,1991.

10. Fingerote RJ, **Bain VG**, Fedorak RN.
Liver transplants for alcoholic liver disease.
Canadian Journal of Gastroenterology 5:195,1991.

11. Lau JYN, **Bain VG**, Smith HM, Alexander GJ, Williams R.
Modulation of hepatitis B viral antigen expression by immunosuppressive drugs in primary hepatocyte culture.
Transplantation 53:894, 1992.

12. Lau JYN **Bain VG**, Davies SE, O'Grady JG, Alberti A, Alexander GJM, Williams R.
High level expression of hepatitis B virus antigens in fibrosing cholestatic hepatitis.
Gastroenterology 102:956,1992.

13. Fingerote RJ, **Bain VG**.
Fulminant hepatic failure.
American Journal of Gastroenterology 88:1000, 1993.

14. Mason AL, Wick M, White HM, Benner KH, Lee RG, Regenstein F, **Bain VG**, Campbell C, Perrillo RP.
Increased hepatocyte expression of hepatitis B virus transcription in patients with features of fibrosing cholestatic hepatitis.
Gastroenterology 105:237, 1993.

15. Duerksen DR, Jewell LD, **Bain VG**.
Hepatic giant cell arteritis and polymyalgia rheumatica.
Canadian Journal of Gastroenterology 8:36, 1994.

16. Ma M, Ryan E, **Bain VG**.
The development of hemochromatosis after treatment for celiac sprue.
Canadian Journal of Gastroenterology 8:358, 1994.

17. Tipples GA, Ma MM, Fischer KP, **Bain VG**, Kneteman NM, Tyrrell DL.
Mutation in HBV RNA-dependant DNA polymerase confers resistance to lamivudine in vivo.

Hepatology 24:714, 1996.

18. Shapiro AMJ, **Bain VG**, Sigalet DL, Kneteman NM.
Rapid resolution of chylous ascites after liver transplantation using somatostatin analog and total.
Transplantation 61:1410, 1996.

19. **Bain VG**, Kneteman NM, Ma MM, Gutfreund K, Shapiro AMJ, Fischer KP, Tipples G, Lee H, Jewell LD, Tyrrell DL.
Efficacy of lamivudine in chronic hepatitis B patients with active viral replication and decompensated cirrhosis undergoing liver transplantation.
Transplantation 62:1456,1996.

20. Duerksen DR, Jewell LD, Mason AL, **Bain VG**.
Co-existence of hepatitis A and adult Reye=s syndrome.
GUT 41:121, 1997.

21. Yoshida EM, Ma MM, Davis JE, Fischer KP, Kneteman NM, Erb SR, Tyrrell LD, **Bain VG**.
Post-liver transplant allograft re-infection with a lamivudine resistant strain of hepatitis B virus: long term follow-up.
Canadian Journal of Gastroenterology 12:125, 1998.

22. Kassam N, **Bain VG.**
Liver transplantation for neuropsychiatric Wilson disease.
Canadian Journal of Gastroenterology 12:65, 1998.

23. Poynard T, Marcellin P, Lee S, Niederau C, Minuk G, Ideo G, **Bain VG**, Heathcote J, Zeuzem S, Trepo C, Albrecht J.
An international randomized trial of interferon alfa-2B and ribavirin 48 or 24 weeks vs interferon alfa-2B 48 weeks, for first line treatment of chronic hepatitis C.
Lancet 352:1426, 1998.

24. Everson GT, Jensen DM, Craig JR, van Leeuwen DJ, **Bain VG**, Ehrinpreis MN, Albert D, John T, Witt K, and the Consensus Interferon Study Group.
Efficacy of interferon treatment for patients with chronic hepatitis C: comparison of response in cirrhotics, fibrotics or nonfibrotics.
Hepatology 30:271, 1999.

25. Wong W, **Bain VG**.
Update in liver transplantation.
Canadian Family Physician 45:1241, 1999.

26. Pockros PJ, **Bain VG**, Hunter EB, Conrad A, Balart LA, Hollinger FB,Albert D, and the Consensus Interferon Study Group.
A comparison of RT-PCR and bDNA assays for hepatitis C virus in patients receiving interferon treatment.

Journal of Viral Hepatitis 6:145, 1999.

27. Shapiro AMJ, **Bain VG**, Preiksaitis JK, Ma MM, Issa S, Kneteman NM.
Oglivie=s syndrome associated with acute cytomegaloviral infection after liver transplantation.
Transplant International 13:41,2000.

28. Gutfreund KS, **Bain VG.**
Chronic viral hepatitis C: Management update.
Canadian Medical Association Journal 162:827, 2000.

29. **Bain VG**, Abraham N, Jhangri GS, Alexander TW, Henning RC, Hoskinson ME, Maguire CG, Lalor EAG, Sadowski DC.
Prospective study of biliary strictures to determine the predictors of malignancy.
Canadian Journal of Gastroenterology 14:397, 2000.

30. Gutfreund KS, Williams M, George R, **Bain VG**, Ma MM, Yoshida EM Villeneuve J-P, Fischer KP, Tyrrell DLJ.
Genotypic succession of mutations of the hepatitis B virus polymerase associated with lamivudine resistance.
Journal of Hepatology 33:469, 2000.

31. Romagnuolo J, Jewell DL, Kneteman NM, **Bain VG**.
Graft-versus-host disease after liver transplantation complicated by systemic aspergillosis with pancarditis.
Canadian Journal of Gastroenterology 14:637, 2000.

32. **Bain VG.**
Hepatitis B in transplantation.
Transplant Infectious Disease 2:153, 2000.

33. **Bain VG**, Montero J-L, de la Mata M.
Bioartificial liver support.
Canadian Journal of Gastroenterology 15:313, 2001.

34. Romagnuolo J, Jhangri GS, Jewell LD, **Bain VG**.
Predicting the liver histology in chronic hepatitis C: How good is the clinician?
American Journal of Gastroenterology 96:3165, 2001.

35. Wong P, Houston S, Power B, Lalor E, **Bain VG**.
A case of histoplasma capsulatum causing granulomatous liver disease and Addisonian crisis.
Canadian Journal of Gastroenterology 15:687, 2001.

36. **Bain VG**.
Effect of HCV viral dynamics on treatment design: lessons learned from HIV.
American Journal of Gastroenterology 96:2818, 2001.

37. Ramji A, Yoshida EM, **Bain VG** et al.
Late Acute Rejection After Liver Transplantation: The Western Canada Experience.
Liver Transplantation 8:945-951, 2002.

38. **Bain VG**, Wong WW, Greig PD and Yoshida EM.
Hepatology and the Canadian Gastroenterologist: Interest, Attitudes and Patterns of Practice. A National Survey from the Canadian Association of Gastroenterology.
Canadian Journal of Gastroenterology 17:25-29, 2002.

39. Abdo AA, **Bain VG**, Kichian K, Lee SS.
Evolution of Autoimmune Hepatitis to Primary Sclerosing Cholangitis: A Sequential Syndrome.
Hepatology 36:1393-1399, 2002.

40. Kichian K, McLean R, Gramlich LM, Bailey RJ, **Bain VG.**
Non-alcoholic Fatty Liver Disease in Patients Investigated for Elevated Liver Enzymes.
Canadian Journal of Gastroenterology 17:38-42, 2003.

41. Greig P, Lilly L, Scudamore C, Erb S, Yoshida E, Kneteman N, **Bain VG**, Ghent C, Marotta P, Grant D, Wall W, Tchervenkov J, Barkun J, Roy A, Marleau D, McAlister V, Peltekian K.
Early steroid withdrawal after liver transplantation: the Canadian tacrolimus versus microemulsion cyclosporin A trial: 1-year follow-up.
Liver Transplantation 9:587-595, 2003.

42. **Bain VG**.
Hepatorenal syndrome, hepatopulmonary syndrome, and now, hepatospinal syndrome?
Liver Transplantation 9:995-996, 2003.

43. Zeuzem S, Heathcote EJ, Shiffman ML, Wright TL, **Bain VG**, Sherman M, Feinman SV, Fried MW, Rasenack J, Sarrazin C, Jensen DM, Lin A, Hoffman JH, Sedarati F.
Twelve weeks of follow-up is sufficient for the determination of sustained virologic response in patients treated with interferon alpha for chronic hepatitis C.
Journal of Hepatology 39:106-11, 2003.

44. Dahlan Y, Smith L, Simmonds D, Jewell LD, Wanless I, Heathcote EJ, **Bain VG**.
Pediatric-onset primary biliary cirrhosis.
Gastroenterology 125:1476-1479, 2003.

45. **Bain VG**, Bonacini M, Govindarajan S, Ma M, Sherman M, Gibas A, Cotler SJ, Deschenes M, Kaita K, Jhangri GS.
A Multicentre study of the usefulness of liver biopsy in hepatitis C.
Journal of Viral Hepatitis 11:375-382, 2004.

46. Kneteman NM, Oberholzer J, Al Saghler M, Meeberg GA, Blitz M, Ma MM, Wong WW, Gutfreund K, Mason AL, Jewell LD, Shapiro AM, **Bain VG**, Bigam DL.

Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma.
Liver Transplantation 10:1301-1311, 2004.

47. Shin JL, Teitel J, Swain MG, **Bain VG**, Adams PC, Croitoru K, Peltekian K, Schweiger F, Simmons M, Heathcote J.
A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with a congenital bleeding disorders and hepatitis C: is it safe and useful?
American Journal Hematology. 78:85-93, 2005.

48. Chatur N, Ramji A, **Bain VG**, Ma MM, Marotta PJ, Ghent CN, Lilly LB, Heathcote EJ, Deschenes M, Lee SS, Steinbrecher UP, Yoshida EM.
Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: the Canadian Association for the Study of Liver (CASL) experience with mycophenolate mofetil and tacrolimus.
Liver International 25:723-27, 2005.

49. Romangnuolo J, Andrews CN, **Bain VG**, Bonacini M, Cotler SJ, Ma M, Sherman M
Simple clinical variables predict liver histology in hepatitis C: prospective validation of a clinical prediction model.
Scandinavian Journal of Gastroenterology 40:1365-71, 2005.

50. Bistritz L, Tamboli C, Bigam D, **Bain VG**
Polycystic liver disease: experience at a teaching hospital.
Am J Gastroenterol. 100:2212-7, 2005.

51. Mason A, Theal J, Adams E, Perrillo R, **Bain VG**
Hepatitis B virus replication in damaged endothelial tissues of patients with extrahepatic disease.
Am J Gastroenterol. 100:972-6, 2005

52. Yoshida EM, Marotta PJ, Greig PD, Kneteman NM, Marleau D, Cantarovich M, Peltekian KM, Lilly LB, Scudamore CH, **Bain VG**, Wall WJ, Roy A, Balshaw RF, Barkun ST.
Evaluation of renal function in liver transplant recipients receiving daclizumab (Zenapax), mycophenolate mofetil, and a delayed, low-dose tacrolimus regimen vs. a standard-dose tacrolimus and mycophenolate mofetil regimen: a multicenter randomized clinical trial.
Liver Transpl. 11:1064-72, 2005.

53. Ghali P, Marotta PJ, Yoshida EM, **Bain VG**, Marleau D, Peltekian K, Metrakos P, Deschenes M.
Liver transplantation for incidental cholangiocarcinoma: Analysis of the Canadian experience.
Liver Transpl. 11:1412-6, 2005.

54. Lee SS, **Bain VG**, Peltekian K, Krajden M, Yoshida EM, Deschenes M, Heathcote J, Bailey RJ, Simonyi S, Sherman M.
Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice.

Aliment Pharmacol Ther. 23:397-408, 2006.

55. **Bain VG,** Kaita KD, Yoshida EM, Swain MG, Heathcote EJ, Neumann AU, Fiscella M, Yu R, Osborn BL, Cronin PW, Freimuth WW, McHutchison JG, Subramanian GM
A phase 2 study to evaluate the antiviral activity, safety, and pharmacokinetics of recombinant human albumin-interferon alfa fusion protein in genotype 1 chronic hepatitis C patients.
J Hepatol. 44:671-8, 2006.

56. Mant MJ, **Bain VG**, Maguire CG, Murland K, Yacyshyn BR.
Prevalence of occult gastrointestinal bleeding in celiac disease.
Clinical Gastroenterol Hepatol. 4:451-4, 2006.

57. Sherman M, Yoshida EM, Deschenes M, Krajden M, **Bain VG**, Peltekian K, Anderson F, Kaita K, Simonyi S, Balshaw R, Lee SS
Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy.
Gut. 55:1631-8, 2006.

58. **Bain VG**, Yoshida EM, Kaita KD, Swain MG, Heathcote EJ, Garcia A, Moore PA, Yu R, McHutchison JG, Subramanian GM.
Dynamics of interferon-specific gene expression in peripheral blood of interferon alfa-naive patients with genotype 1 chronic hepatitis C infection treated with albumin-interferon alfa.
Hepatol Res. 35:256-62, 2006.

59. Zeman M, Campbell P, **Bain VG**.
Hepatitis C eradication and improvement of cryoglobulinemia-associated rash and membranoproliferative glomerulonephritis with interferon and ribavirin after kidney transplantation.
Can J Gastroenterol. 20:427-31, 2006.

60. Bistritz L, **Bain VG**.
Sphincter of Oddi dysfunction: Managing the patient with chronic biliary pain.
World J Gastroenterology, 12:3793-3802, 2006.

61. Al-Saif F, Al-Masloom A, Johnson MA, **Bain VG**, Sandha GS, Ritchie DB, Shapiro AM.
Autoimmune pancreatitis with autoimmune hemolytic anemia.
Pancreas. 33:316-7, 2006.

62. McDermid J, Chen M, Li Y, Wasilenko S, Bintner J, McDougall C, Pang X, **Bain VG**, Mason AL.

Reverse transcriptase activity in patients with primary biliary cirrhosis and other autoimmune liver disorders.
Aliment Pharmacol Therapy 26:587-595, 2007.

63. Toso C, Al-Qahtani M, Alsaif FA, Bigam DL, Meeberg GA, Shapiro AM, **Bain VG**, Kneteman N.

ABO-incompatible liver transplantation for critically ill adult patients.
Transplant International, 20:675-681, 2007.

64. Tandon P, Rowe BH, Vandermeer B, **Bain VG**.
The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus.
Am J Gastroenterol 102:1528-1536, 2007.

65. Tandon P, **Bain VG**, Tsuyuki T, Klarenbach S.
Systematic review: renal and other clinically relevant outcomes in hepatorenal syndrome.
Aliment Pharmacol Ther 25:1017-1028, 2007.

66. Toso C, Meeberg G, Bigam DL, Oberholzer J, Shapiro AMJ, Gutfreund K, Ma, MM, Mason AL, Wong WS, **Bain VG**, Kneteman N.
De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects.
Transplantation, 83:1162-1168, 2007.

67. Chatterjee A, Swain MG, Lee SS, **Bain VG**, Peltekian K, Croitoru K, Adams PC, Kaita K, Teitel J, Heathcote EJ.
Induction versus noninduction antiviral therapy for chronic hepatitis C virus in patients with congenital coagulation disorders: a Canadian multicentre trial.
Can J Gastroenterol, 21:91-96, 2007.

68. Demeria D, Birchall I, **Bain VG**.
Dramatic reduction in tumor size in hepatocellular carcinoma patients on thalidomide therapy.
Can J Gastroenterol, 21:517-518, 2007.

69. Powis J, Peltekian KM, Lee SS, Sherman M, **Bain VG**, Cooper C, Krajden M, Deschenes M, Balshaw RF, Heathcote EJ, Yoshida EM.
Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3.
Journal of Viral Hepatitis (in press).

70. Karvellas C, Gibney N, Kutsogiannis D, Wendon J, **Bain VG**.
Bench-to-bedside review: current evidence for extracorporeal albumin dialysis systems in liver failure.
Critical Care, 11:215, 2007.

71. Tandon P, Tsuyuki RT, Mitchell L, Hoskinson M, Ma MM, Wong WW, Mason AL, Gutfreund K, **Bain VG**
The effect of 1 month of therapy with midodrine, octreotide-LAR and albumin in refractory ascites: a pilot study.
Liver International, 19, 2008

72. Romagnuolo J, Hilsden R, Sandha GS, Cole M, Bass S, May G, Love J, **Bain VG,** McKaigney J, Fedorak RN
Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized placebo-controlled trial.
Clinical Gastroenterology Hepatology, 6:4, 465-71, 2008

73. Zeuzem S, Yoshida EM, Benhamou Y, Pianko S, **Bain VG,** Shouval D, Flisiak R, Rehak V, Grigorescu M, Kaita K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG
Albinterferon alfa-2b dosed every two or four weeks in interferon-naïve patients with genotype 1 chronic hepatitis C.
Hepatology, 48:2, 407-17, 2008

74. Alhayaf N, Lalor E, **Bain VG,** McKaigney J, Sandha GS
The clinical impact and cost implication of endoscopic ultrasound on use of endoscopic retrograde cholangiopancreatography in a Canadian university hospital.
Canadian Journal of Gastroenterology, 22:2, 138-42, 2008

75. Powis J, Peltekian KM, Lee SS, Sherman M, **Bain VG,** Cooper C, Krajden M, Deschenes M, Balshaw RF, Heathcote EJ, Yoshida EM, Canadian Pegasys Study Group Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3.
Journal of Viral Hepatology, 15:1, 52-7, 2008

76. Kroeker KI, **Bain VG,** Shaw-Stiffel T, Fong TL, Yoshida EM
Adult liver transplant survey: policies towards eligibility criteria in Canada and the United States 2007.
Liver International, 28:9, 1250-5, 2008

77. **Bain VG,** Lee SS, Peltekian K, Yoshida EM, Deschênes M, Sherman M, Bailey R, Witt-Sullivan H, Balshaw R, Krajden M, Canadian PEGASYS Study Group
Clinical trial: exposure to ribavirin predicts EVR and SVR in patients with HCV genotype 1 infection treated with peginterferon alpha-2a plus ribavirin.
Aliment Pharmacology Therapy, 29:1, 43-50, 2008

78. **Bain VG,** Kaita KD, Marotta P, Yoshida EM, Swain MG, Bailey RJ, Patel K, Cronin PW, Pulkstenis E, McHutchison JG, Subramanian GM
Safety and antiviral activity of albinterferon alfa-2b dosed every four weeks in genotype 2/3 chronic hepatitis C patients.
Clinical Gastroenterology Hepatology, 6:6, 701-6, 2008

79. Cooper CL, Bailey RJ, **Bain VG,** Anderson F, Yoshida EM, Krajden M, Marotta P, Canadian Pegasys Study Group
Outcomes of peginterferon alpha-2a and ribavirin hepatitis C therapy in Aboriginal Canadians.
Canadian Journal of Gastroenterology, 22:8, 677-80, 2008

80. Rozenberg L, **Bain VG**, McHutchison JG, Pulkstenis E, Subramanian GM, Neumann AU
Pharmacodynamics and viral kinetics during albinterferon alfa-2b therapy of chronic hepatitis C genotype 1 treatment-naive patients.
The Journal of Medicine, 1:1, 2008

81. Montano-Loza AJ, Mason AL, Ma M, Bastiampillai RJ, **Bain VG**, Tandon P
Risk factors for recurrence of autoimmune hepatitis after liver transplantation.
Liver Transplantation, 15:10, 1254-61, 2009

82. Montano-Loza AJ, Tandon P, Kneteman N, Bailey R, **Bain VG**
Rotterdam score predicts early mortality in Budd-Chiari Syndrome, and surgical shunting prolongs transplant-free survival.
Aliment Pharmacol Therapy, 30:10, 1060-1069, 2009

83. Karvellas CJ, Bagshaw SM, McDermid RC, Stollery DE, **Bain VG**, Gibney RT
A case-control study of single-pass Albumin dialysis for acetaminophen-induced acute liver failure.
Blood Purification, 28:3, 151-8, 2009

84. Tandon P, Moncrief K, Madsen K, Arrieta MC, Owen RJ, **Bain VG**, Wong WW, Ma MM
Effects of probiotic therapy on portal pressure in patients with cirrhosis: a pilot study.
Liver International, 29:7, 1110-5, 2009

85. Tandon P, Goodman KJ, Ma MM, Wong WW, Mason AL, Meeberg G, Bergsten D, Carbonneau M, **Bain VG**
A shorter duration of pre-transplant abstinence predicts problem drinking after liver transplantation.
Am J Gastroenterology, 104:7, 1700-6, 2009

86. Yoshida EM, Sherman M, **Bain VG**, Cooper CL, Deschênes M, Marotta PJ, Lee SS, Krajden M, Witt-Sullivan H, Bailey R, Usaty C, Peltekian K, Pegasys Study Group
Re-treatment with Peginterferon alfa-2a and Ribavirin in patients with chronic hepatitis C who have relapsed or not responded to a first course of Pegylated Interferon-based therapy.
Canadian Journal of Gastroenterology, 23:3, 180-4, 2009

87. Fouad TR, Abdel-Razek WM, Burak KW, **Bain VG**, Lee SS
Prediction of cardiac complications after liver transplantation.
Transplantation, 87:5, 763-70, 2009

88. Neumann AU, **Bain VG**, Yoshida EM, Patel K, Pulkstenis E, Subramanian GM
Early prediction of sustained virological response at day 3 of treatment with Albinterferon-Alpha-2b in patients with genotype 2/3 chronic hepatitis C.
Liver International, 29:9, 1350-5, 2009

89. Carbonneau M, Jensen LA, **Bain VG**, Kelly K, Meeberg G, Tandon P
Alcohol use while on the liver transplant waiting list – a single center experience.
Liver Transplantation, 16:91-97, 2010

90. Asthana S, Maguire C, Lou L, Meier M, **Bain V**, Townsend R, Lien D, Bigam D, Kneteman N, Shapiro A.
Successful resolution of severe hepatopulmonary syndrome following liver transplantation.
Transplant International, 23:432-435, 2010

91. Moncreif KJ, Savu A, Ma MM, **Bain VG**, Wong WW, Tandon P.
The natural history of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation – a single centre experience.
Canadian Journal Gastroenterology, 24:1, 40-6, 2010

92. Emamaullee JA, Edgar R, Toso C, Thiesen A, **Bain V**, Bigam D, Kneteman N, Shapiro AM.
Vascular endothelial growth factor expression in hepatic epithelioid hemangioendothelioma: Implications for treatment and surgical management.
Liver Transplantation, 16:191-197, 2010

93. Deschenes M, **Bain VG**, Lee SS, Sherman M, Cooper CL, Yoshida EM, Marotta PJ, Krajden M, Usaty C, Balshaw R, Peltekian KM, Canadian Pegasys Study Group.
Identifying HCV genotype 1 patients at risk of relapse.
European Jouranl Gastroenterology Hepatology, 22:5, 546-51, 2010

94. Meza-Junco J, Montano-Loza AJ, Ma M, Wong W, Sawyer MB, **Bain VG**.
Cholangiocarcinoma: has there been any progress?
Canadian Journal Gastroenterology, 24:1, 52-7, 2010

95. Nelson DR, Benhamou Y, Chuang WL, Lawitz EJ, Rodriguez-Torres M, Flisiak R, Rasenack JW, Kryczka W, Lee CM, **Bain VG**, Pianko S, Patel K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG, ACHIEVE-2/3 Study Team.
Albinterferon Alfa-2b was not inferior to pegylated interferon-? in a randomized trial of patients with chronic hepatitis C virus genotype 2 or 3.
Gastroenterology, 139:4, 1267-76, 2010

96. Jayakumar S, **Bain V**.
Rational Guide to the Use of Erythropoietin in the Treatment of HCV Infection.
Current Hepatitis Reports 10:62-69, 2011

97. Peltekian KM, **Bain VG**, Lee SS, Sherman M, Cooper CL, Yoshida EM, Marotta PJ, Krajden M, Balshaw R, Deschênes M.
Is pre-treatment liver biopsy necessary for all hepatitis C genotypes?
Annals Hepatology 10:260-9, 2011

98. Chopra A, Cantarovich M, **Bain VG**.
Simultaneous liver and kidney transplants: optimizing use of this double resource.
Transplantation 91:1305-9, 2011

99. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, **Bain VG**, Sawyer MB.
Muscle Wasting Is Associated With Mortality in Patients With Cirrhosis.
Clinical Gastroenterology and Hepatology 10:166-73, 2012

100. Meza-Junco J, Montano-Loza AJ, Liu DM, Sawyer MB, **Bain VG**, Ma M, Owen R.
Locoregional radiological treatment for hepatocellular carcinoma; Which, when and how?
Cancer Treat Review 38:54-62, 2012

101. Montano-Loza AJ, Vargas-Vorackova F, Ma M, **Bain VG**, Burak K, Kumar T, Mason AL.
Incidence and risk factors associated with de novo autoimmune hepatitis after liver transplantation.
Liver International 32(9): 1426-33, 2012

102. Ye C, Saincher M, Tandon P, Meeburg G, Williams R, Burak KW, **Bain VG**.
Cardiac work-up protocol for liver transplant candidates: experience from a single liver transplant centre.
Canadian Journal of Gastroenterology 26(11) :806-810, 2012

103. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, **Bain VG**, Esfandiari N, Baracos V, Montano-Loza AJ, Myers RP.
Severe muscle depletion in patients on the liver transplant wait list : its prevalence and independent prognosis value.
Liver Transplantation 18(10) : 1209-16, 2012

104. Lambert JE, **Bain VG**, Ryan EA, Thomson AB, Clandinin MT.
Elevated lipogenesis and diminished cholesterol synthesis in patients with hepatitis C viral infection compared to healthy humans.
Hepatology 57(5) :1697-1704, 2013

105. Alameel T, **Bain VG**, Sandha G.
Clinical application of a single-operator direct visualization system improves the diagnostic and therapeutic yield of endoscopic retrograde cholangiopancreatography.
Canadian Journal of Gastroenterology 27(1):15-9, 2013.

106. Kao D, Zepeda-Gomez S, Tandon P, **Bain VG.**
Managing the post-liver transplantation anastomotic biliary stricture: multiple plastic versus metal stents: a systematic review.
Gastrointestinal Endoscopy 77(5):679-91, 2013.

107. Al-Judaibi B, **Bain VG**, Sis B.
An unusual cause of elevated liver enzymes in a diabetic patient.
Gastroenterology 144(7):1354, 1577-8, 2013.

108. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, **Bain VG**, Beaumont C, Esfandiari N, Lieffers JR, Sawyer MB.
Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma
Journal of Clinical Gastroenterology 47(10): 861-870, 2013

109. Jayakumar S, Carbonneau M, Hotte N, Befus AD, St Laurent C, Owen R, McCarthy M, Madsen K, Bailey RJ, Ma M, **Bain V**, Rioux K, Tandon P
VSL#3 probiotic therapy does not reduce portal pressures in patients with decompensated cirrhosis
Liver International 33(10):1470-7, 2013

110. Wells MM. Roth LS. Marotta P. Levstik M. Mason AL. **Bain VG**. Chandok N. Aljudaibi BM.
Increased duration of dual pegylated interferon and ribavirin therapy for genotype 1 hepatitis C post-liver transplantation increases sustained virologic response: a retrospective review
Saudi Journal of Gastroenterology. 19(5):223-9, 2013.

B. Book Chapters and Invited Contributions

1. **Bain VG** and Thomson ABR.
The safety and effectiveness of misoprostol in the treatment of duodenal ulcer.
Internal Medicine for the Specialist 8:73, 1987.

2. **Bain VG** and Thomson ABR.
Update in Small Bowel Disease.
In: Current Gastroenterology Vol 8, Editor G. Gitnick, 1988.

3. **Bain VG** and Thomson ABR.
Gastrointestinal and hepatic complications in the intensive care unit.
Medicine North America 18:3524, 1988.

4. **Bain VG**, Alexander GJM, Eddleston ALWF.
Viral Hepatitis.
In: Immunology and Immunopathology of the Liver and Gastrointestinal Tract.
Eds. Targan S.R. and Shanahan F. 1990.

5. **Bain VG**, Minuk GY.
Jaundice, ascites and hepatic encephalopathy. In:
Oxford Textbook of Palliative Care, Oxford University Press 1993.

6. **Bain VG** (Ed), Depew W, Steinbrecher U.
Hepatitis Update. Would you treat this patient? A debate regarding controversial aspects of chronic hepatitis C and its management.
Canadian Journal of Gastroenterology 10:81, 1996.

7. **Bain VG.**
Hepatitis Update. Literature Review - Hepatitis C current findings - What=s new?
Canadian Journal of Gastroenterology 11:141, 1997.

8. **Bain VG.**
Jaundice, ascites and hepatic encephalopathy.
In: Oxford Textbook of Palliative Medicine,
Oxford University Press, 1997.

9. **Bain VG**, Ma M.
Acute Viral Hepatitis.
In: First Principles of Gastroenterology, Third Ed. Eds, Thomson ABR, Shaffer E, 1997.

10. **Bain VG**, Ma M.
Chronic Hepatitis.
In: First Principles of Gastroenterology, Third Ed. Eds, Thomson ABR, Shaffer E, 1997.

11. **Bain VG.**
Hepatitis C - What does the future hold? (Editorial)
Canadian Journal of Gastroenterology 14:571, 2000.

12. **Bain VG** and Ma M.
Acute Viral Hepatitis
In: First Principles of Gastroenterology, Fourth Ed. Eds. Thomson ABR, Shaffer E, 2000.

13. **Bain VG** and Ma M.
Chronic Hepatitis
In: First Principles of Gastroenterology, Fourth, Ed. Eds. Thomson ABR, Shaffer E, 2000.

14. Lam E and **Bain VG**.
Hepatitis as a World Health Problem.
Encyclopaedia of Life Sciences, Nature Publishing Group, 2001 (www.els.net).

15. Kichian K and **Bain VG.**
Jaundice, ascites and hepatic encephalopathy.
In: Oxford Textbook of Palliative Medicine Oxford University Press 2003.

16. Grover P, **Bain VG**.
Chronic hepatitis.
In: First Principles of Gastroenterology, Fifth Ed. Eds. Thomson ABR, Shaffer E,
2005.

17. **Bain VG.**
Exciting experimental therapies in acute liver failure.
Gastroenterology Canada, Vol 7(3), 2005.

18. **Bain VG**, Tandon P.
Hepatitis as a World Health Problem.
In: Encyclopedia of Life Sciences, Nature Publishing Group, 2006 (www.els.net).

19. **Bain VG**, Tandon P.
Hepatitis as a World Health Problem.
Encyclopedia of Life Sciences, John Wiley & Sons, Ltd: Chichester
http:///www.els.net/[doi:10.1002/9780470015902.a0002236.pub2], 2007.

C. Group Publications

1. **Canadian Association for the Study of the Liver: Hepatitis Consensus Group.**
Treatment of Chronic Viral Hepatitis with Alpha-Interferon: A Consensus Conference Report.
Canadian Journal Gastroenterology 8:179, 1994 and Canadian Journal of Infectious Diseases 5:107, 1994.

2. **The North American Crohn's Study Group Investigators.**
Methotrexate for the treatment of Crohn's disease.
New England Journal of Medicine 332:292, 1995.

3. **Canadian Association for the Study of the Liver Hepatitis Consensus Group.**
Management of viral hepatitis: clinical and public health perspectives - A consensus statement.
Canadian Journal of Gastroenterology 11:407, 1997.

4. Keefe EB, Hollinger FB and **The Consensus Interferon Study Group.**
Therapy of hepatitis C: Consensus interferon trials.
Hepatology 26 (Suppl.)101S, 1997.

5. Tong MJ and **the Consensus Interferon Study Group.**
Treatment of chronic hepatitis C with consensus interferon: A multicentre randomized controlled trial.
Hepatology 26:747, 1997.

6. Heathcote JE, Keefe EB, Lee SS and **the Consensus Interferon Study Group**
Re-treatment of chronic hepatitis C with consensus interferon.
Hepatology 27:1136, 1998.

7. Grant D, Kneteman N, Roy A and **the Canadian Liver Transplant Study Group.**
Peak cyclosporin levels correlate with freedom from liver graft rejection: results of a prospective randomized comparison of neoral and sandimmune for liver transplantation.
Transplantation 67:1133, 1999.

8. Keeffe EB, Dusheiko GM, Tong MJ and **the Consensus Interferon Study Group.**
Genotype does not affect pattern of HCV RNA decrease among responders during interferon

treatment of chronic hepatitis.
Cytokines, Cellular & Molecular Therapy 5:211, 1999.

9. Keeffe EB, Dusheiko GM, James SP and **the Consensus Interferon Study Group**.
Utility of hepatitis C virus serotypes in predicting response to treatment of chronic hepatitis C.
Cytokines, Cellular & Molecular Therapy 5:207, 1999.

10. Grant D, Kneteman N, Tchervenkov J, Roy A, Murphy G, Tan A, Hendricks L, Giulbault N, Levy G.
Peak cyclosporine levels (C max) correlate with freedom from liver graft rejection.
Transplantation 67:1133-1999.

11. Heathcote JE, James S, Mullen KD, Hauser SC, Rosenblate H, Albert Jr DG and **the Consensus Interferon Study Group.**
Chronic hepatitis C virus patients with breakthroughs during interferon treatment can successfully be retreated with consensus Interferon.
Hepatology 30: 562-1999.

12. Wong F, Blei AT, Blendis LM, Thuluvath PJ, for **The North American VPA-985 Study Group.**
A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized placebo-controlled trial.
Hepatology 37:182-190, 2003.

13. Sherman M, **Bain VG**, Villeneuve J-P, Myers RP, Cooper C, Martin S, Lowe C.
The management of chronic viral hepatitis: A Canadian Consensus Conference, www.hepatology.ca, 2004, and Canadian Journal of Gastroenterology 18:715-728, 2004

14. Angeli P, Wong F, Watson H, Gines P and the CAPPS Investigators.
Hyponatremia in cirrhosis: results of a patient population survey.
Hepatology, 44:1535-1542, 2006.

D. Abstracts & Brief Communications (1-100 Thinned – available on request)

101. Chatur N, Ramji A, **Bain VG**, Ma M, Marotta P, Ghent C, Lilly L, Heathcote EJ, Deschenes M, Steinbrecher U, Yoshida E.
Transplant immunosuppressive agents in non-transplant chronic autoimmune hepatitis: The CASL experience with mycophenolate mofetil and Tacrolimus,
American Gastroenterology Association, Feb; M1982, 2004.
Canadian Journal of Gastroenterology. Sep;18:(Suppl A):94A, 2004.

102. Kichian K, Gerhardt A, Gutfreund K, Jewell L, Ma M, Mason AL, Mulesa L, Wong W, **Bain VG**.
The role of the glucose challenge test in the evaluation of patients with non-alcoholic fatty liver disease.

Canadian Journal of Gastroenterology, 18:93A (Suppl A), 2004.

103. Bistritz L, Tamboli C, **Bain VG**.
Polycystic liver disease: Experience at a teaching hospital.
Canadian Journal of Gastroenterology, 18: 93A (Suppl A), 2004.

104. Teitel J, Heathcote EJ, Shin J, Swain MG, **Bain VG**, Adams PC, Croitoru K, Peltekian K, Schweiger F, and Simons ME.
A Canadian multicenter study evaluating transjugular liver biopsy in patients with hepatitis C and congenital bleeding disorders.
Haemophilia. March 10: 46-50 (Suppl 3), 2004.

105. Shin J, Teitel J, Swain M, **Bain VG**, Peltekian K, Croitoru K, Adams P, Simons M, Heathcote EJ.
Risks and benefits of transjugular liver biopsy in patients with congenital coagulation disorders.
Can J Gastroenterol. Feb;18: 87A (Suppl A), 2004.

106. Kichian K, Gerhardt A, Gutfreund K, Jewell L, Ma M, Mason A, Mulesa L, Wong W, **Bain VG**.
The role of the glucose challenge test in the workup of patients with non alcoholic fatty liver disease.
American Gastroenterology Association, T1100, 2004,
Can J Gastroenterol. Feb;18: 93A (Suppl A), 2004.

107. Mathew G, Meeberg G, **Bain VG**, Lalor E, McKaigney J, Kneteman N, Sandha G.
Endoscopic therapy of biliary strictures after orthotopic liver transplantation.
Can J Gastroenterol. 18:(Suppl A):85A, 2004.

108. Feinman SV, **Bain VG**, Peltekian K, Marotta P, Deschenes M.
Efficacy and safety of peginterferon alfa-2a in combination with ribavirin in Canadian patients with chronic hepatitis C: Interim results in cirrhotic and non-cirrhotic patients.
Can J Gastroenterol. Feb;18:(Suppl A):84A, 2004

109. Bain VG.
Clinical trials registry (letter).
Canadian Medical Association Journal 172:979-80, 2005

110. Rozenberg L, **Bain VG**, Neumann AU.
HCV kinetics as function of albuferon pharmacodynamics in subjects with genotype 1 chronic hepatitis C.
12th International Symposium on HCV and Related Viruses, Montreal, Oct 2-6, 2005, Hepatology 2005.

111.Bain VG, Kaita K, Yoshida E, Swain M, Heathcote J, McHutchison J, Neumann A, Bagchi P, Osborn B, Cronin P, Novello L, Freimuth W, Subramanian M.
A phase 2 study to assess antiviral response, safety, and pharmacokinetics of albuferon in IFN-alpha naïve subjects with genotype 1 hepatitis C.
40th Annual Meeting of EASL, Paris, France, Apr 13-17, 2005, Journal of Hepatology

42:(Supplement):9, 2005.

112. Sherman M, Yoshida E, Deschenes M, Krajden M, **Bain VG**, Peltekian K, Anderson F, Kaita K, Simonyi S, Lee S.
Peginterferon alpha-2a (40 kDa) plus ribavirin in chronic hepatitis C patients who failed previous interferon-based therapy: results of a multicenter open-label expanded access program in Canada.
40th Annual Meeting of EASL, Paris, France, Apr 13-17, 2005, Journal of Hepatology.
42:(Supplement):220, 2005.

113. Lee S, **Bain VG**, Peltekian K, Krajden M, Yoshida E, Deschenes M, Heathcote EJ, Bailey R, Simonyi S, Sherman M.
Peginterferon alpha-2a (40 kDa) plus ribavirin in cirrhotic patients with chronic hepatitis C: results of a Canadian Multicentre open-label expanded access program. 2005, Journal of Hepatology 42:(Supplement):209, 2005.

114. Johnson M, **Bain VG**, Bigam D, Gutfreund K, Kneteman N, Mason A, Meeberg G, Shapiro J, Wong W, Ma M.
Liver transplantation for hepatocellular carcinoma: the significance of microvascular invasion and factors associated with cancer recurrence post-liver transplant.
World Congress of Gastroenterology, Sept 10-14, Montreal, QC, 2005.

115. Yoshida E, Heathcote J, Bailey R, Anderson F, Kaita K, Krajden M, Deschenes M, **Bain VG**, Lee S, Sherman M, Peltekian K, Simoni S.
"Real World": experience with peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C: results of a multicenter open-label expanded access program in Canada.
Gastroenterology 128(4, Suppl 2):A723, 2005.

116. Grover PT, Kneteman N, Shapiro J, Bigam D, Ma M, Mason A, Wong W, **Bain VG**, Gutfreund K.
Rapid intrahepatic recurrence of hepatic mangioendothelioma after living donor liver transplantation.
CASL, March, Banff, 2005.

117. Peltekian K, Deschenes M, Lee S, **Bain V**, The Canadian Pegasys Study Group.
Predictability of early virological response to peginterferon alfa-2A (40KD) plus ribavirin in the "Real World".
CASL, March, Banff, 2005.

118.Bain V, Kaita K, Yoshida E, Swain M, Heathcote J, McHutchinson J, Garcia A, Bagchi P, Cronin P, Novello L, Freimuth W, Moor P, Subramanian M.
Interferon specific gene expression mediated by albuferon in IFNA naïve subjects and correlation with anti-viral response.
CASL, March, Banff, 2005.

119. Peltekian K, Deschenes M, Lee S, **Bain V**, The Canadian Pegasys Study Group.
Predictability of early virological response to peginterferon alfa-2A (40KD) plus ribavirin in the

"Real World".
Gastroenterology 128:(4, Suppl 2):A-721, 2005.

120. Burak K, Meeberg G, Myers R, Hilsden R, Swain M, Wong W, Fick G, **Bain VG.**
Should Canada adopt the MELD score for allocation of liver transplants?
Can J Gastroenterol 20:194, 2006.

121. Cooper C, Bailey R, **Bain VG**, Anderson F, Marotta P.
Canada's first nations with chronic hepatitis C: therapeutic outcomes of the pegasys expanded access program.
Can J Gastroenterol 20:197, 2006.

122. Powis J, Peltekian K, Lee S, Sherman M, **Bain VG**, Cooper C, Krajden M, Balshaw R, Heathcote J, Yoshida.
Is it time to separate the management of genotype 2 and genotype 3 in chronic hepatitis C?
Can J Gastroenterol 20:207, 2006.

123.Bain VG, Lee SS, Peltekian K, Yoshida E, Deschênes M, Sherman M, Bailey R, Witt-Sullivan H, Balshaw R, Krajden M.
Exposure to ribavirin (RBV) predicts EVR and SVR in patients with HCV genotype 1 infection: analysis of the Canadian pegasys expanded access program (EAP).
Hepatology 44:335A, 2006.

124. McHutchison J, Zeuzem S, Benhamou Y, Shouval D, **Bain VG**, Pianko S et al.
Interim antiviral and safety data with albumin interferon alfa-2B combined with ribavirin in a phase 2B study conducted in a genotype 1, IFN-naïve, chronic hepatitis C population.
Hepatology 44:614A, 2006.

125. Grover PT, Rowe BH, Vandermeer B, **Bain VG.**
The efficacy and safety of bile acid binding agents, opioid antagonists or rifamipin in the treatment of cholestasis associated pruritus.
Hepatology 44:636A, 2006.

126. Nudo C, **Bain VG**, Marleau D, Marotta P, Wong P, Yoshida E et al.
Liver transplantation for hepatic epitheliod hemangioendothelioma and neuroendocrine tumors: the Canadian multicenter experience.
Hepatology 44:411A, 2006.

127. Fiscella M, Balan V, Nelson D, **Bain VG**, Zeuzem S, McHutchison J et al.
Favorable pharmacokinetics of albumin interferon alfa in subjects with chronic hepatitis C.
Hepatology 44:613A, 2006.

128. Zeuzem S, Benhamou Y, **Bain VG**, Shouval D, Pianko S, Flisiak R, Grigorescu M, Rehak V, Yoshida E, Kaia K, Cronin P, Pulkstenis E, Subramanian M, McHutchison J.
Antiviral response at week 12 following completion of treatment with albinterferon α2b plus

ribavirin in genotype 1, IFN-naïve, chronic hepatitis C patients.
J Hepatol 46(Suppl 1):S293, 2007.

129. Deschênes M, Yoshida E, Peltekian K, Cooper C, **Bain VG**, Krajden M, Sherman M, Lee SS, Balshaw R, Marotta P.
Management of chronic hepatitis C in a diverse population with peginterferon α-2a and ribavirin: final results of the Canadian pegasys expanded access program (EAP).
J Hepatol 46(Suppl 1):S232, 2007.

130. Bain VG, Marotta P, Kaita K, Yoshida E, Swain M, Bailey R, Neumann A, Cronin P, McHutchison J, Pulkstenis E, Subramanian M.
Comparable antiviral response rates with albumin interferon alfa-2b dosed at Q2W or Q4W intervals in naïve subjects with genotype 2 or 3 chronic hepatitis C.
J Hepatol 46(Suppl 1):S7, 2007.

131.Bain VG, Lee SS, Peltekian K, Yoshida E, Deschênes M, Sherman M, Bailey R, Witt-Sullivan H, Balshaw R, Krajden M.
Exposure to ribavirin (RBV) predicts EVR and SVR in patients with HCV genotype 1 infection: analysis of the Canadian pegasys expanded access program (EAP).
Can J Gastroenterol, 21(Suppl A):155A, 2007.

132. Zeman M, Meeberg G, Belland D, **Bain VG**, Bigam D, Grover P, Gutfreund K, Kneteman N, Mason A, Shapiro J, Wong W, Ma M.
The impact of nutritional status on prediction of outcome in patients awaiting and following liver transplantation.
Can J Gastroenterol 21(Suppl A):146A, 2007.

133. Deschênes M, Lee SS, Cooper C, Marotta P, **Bain VG**, Sherman M, Scully L, Wong D, Balshaw R, Peltekian K.
Is it possible to identify HCV genotype 1 patients at risk of relapse? Analysis of the Canadian Pegasys expanded access program (EAP).
Can J Gastroenterol 21(Suppl A):78A, 2007.

134. Pianko S, Yoshida EM, Zeuzem S, Benhamou Y, **Bain VG**, Pulkstenis E, McHutchison JG, Subramanian GM.
Favorable quality of life (QOL) with albinterferon alfa-2b plus ribavirin in genotype 1, IFN-naïve, chronic hepatitis C (CHC) patients.
Hepatology, 46(Suppl 1):822A, 2007.

135. Zeuzem S, Yoshida EM, Benhamou Y, **Bain VG**, Shouval D, Pianko S, Flisiak R, Grigorescu M, Rehak V, Kaita KD, Cronin P, Pulkstenis E, Subramanian GM, McHutchison JG.
Sustained virologic response rates with albinterferon alfa-2B plus ribavirin treatment in IFN-naive, chronic hepatitis C genotype 1 patients.
Hepatology, 46(Suppl 1):317A, 2007.

136. Romagnuolo J, Hilsden R, Sandha GS, Cole M, Bass S, May G, Love J, **Bain VG,** McKaigney J, Fedorak RN
Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized placebo-controlled trial.
Clinical Gastroenterology Hepatology, 6:4, 465-71, 2008

137. Stephen Pianko, Eric M. Yoshida, Stefan Zeuzem, Yves Benhamou, **Vincent G. Bain**, et al
Health-Related Quality of Life (HRQOL) with Albinterferon Alfa-2b Plus Ribavirin in IFN Treatment-Naive Patients with Genotype 1 Chronic Hepatitis C.
Gastroenterology, 134:4, 787A, 2008

138. Adivan U. Neumann, Lynn Rozenberg, **Vincent G. Bain,** John G. McHutchison, et al
Viral Kinetics and Pharmacodynamics of Albinterferon Alfa-2b in Interferon Treatment-Naive Patients with Genotype 1, Chronic Hepatitis C.
Gastroenterology, 134:4, 788A, 2008

139. Puneeta Tandon, Karen J. Goodman, Mang M. Ma, Winnie Wong, Andrew L. Mason, Glenda Meeberg, Donna Bergsten, Michelle Carbonneau, **Vincent G. Bain**
The Duration of Pre-Transplant Abstinence is an Independent Predictor of Problem Drinking Post Liver Transplantation
Hepatology, 48:4, 555A-556A, 2008

140. Aldo J. Montano-Loza, Andrew L. Mason, Mang M. Ma, **Vincent G. Bain,** et al
Risk Factors for Recurrene of Autoimmune Hepatitis After Liver Transplantation
Hepatology, 48:4, 1091A-1092A, 2008

141.P Tandon, KJ Goodman, G Meeburg, D Bergstrom, C Hoekstra, M Carbonneau, **VG Bain**
The Duration of Pre-Transplant Abstinence is an Independent Predictor of Problem Drinking Post Liver Transplantation
Gastroenterology, 22, 132A, 2008

142.KI Kroeker, **VG Bain,** T Shaw-Stiffel, T. Fong, et al
Adult Liver Transplant Survey: Policies Towards Eligibility Criteria in Canada and the United States in 2007
Gastroenterology, 22, 125A, 2008

143.P. Tandon, RT Tsuyuki, L. Mitchell, M. Hoskinson, MM Ma, WW Wong, AL Mason, K Gutfreund, **VG Bain**
The Effect of Midodrine, Octreotide and Albumin in Refractory Ascites
Gastroenterology, 22, 120A, 2008

144.J Romagnuolo, R Hilsden, GS Sandha, M Cole, S Bass, G May, J Love, **VG Bain,** J McKaigney, RN Fedorak
Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP): Final Results from a randomized multi-centered placebo-controlled trial

Gastroenterology, 22, 79A, 2008

145.TR Fouad, AAM Shaheen, KW Burak, **VG Bain**, et al
Prediction of Cardiac Complications After Liver Transplantation
Gastroenterology, 22, 81A, 2008

146.K. Moncrief, A. Savu, MM Ma, **VG Bain**, P. Tandon
The Course of Inflammatory Bowel Disease (IBD) and Primary Sclerosing Cholangitis (PSC) After Liver Transplantation for PSC
Gastroenterology, 22, 90A, 2008

147.Y. Benhamou, S. Zeuzem, E. Yoshida, **V. Bain**, et al
Sustained Virologic Response with Albuinterferon Alfa-2b Plus Ribavirin Treatment in IFN-Naïve, Chronic Hepatitis C Genotype 1 Patients
Hepatology International, 2, A167, 2008

148.V. Bain, K. Kaita, P. Marotta, E. Yoshida, M. Swain, R. Bailey, K. Patel, P. Cronin, E. Pulkstenis, J. Mchutchison, M. Subramanian
Albinterferon Alfa-2b Dosed at 4-Week Intervals Demonstrates Clinically Meaningful Antiviral Activity in Chronic Genotype 2 or 3 Hepatitis C Virus Infection: Results of a Phase 2 Study
Hepatology International, 2, A168, 2008

149. Kroeker KI, **Bain VG,** Shaw-Stiffel T, Fong TL, Yoshida EM
Adult liver transplant survey: policies towards eligibility criteria in Canada and the United States 2007
Liver International, 28:9, 1250-55, 2008

150. Nelson D, Benhamou Y, Chuang WL, Lawitz E, Flisiak R, Rodriguez-Torres M, **Bain VG**, Patel K, Cronin PW, Pulkstenis E, Subramanian GM, McHutchison JG
Efficacy and safety results of albinterferon alfa-2B in combination with ribavirin in interferon-alfa treatment naïve patients with genotype 2 or 3 chronic hepatitis C
Journal of Hepatology, 50:1, S378, 2009

151. Sulkowski MS, Zeuzem S, Lawitz E, Grigorescu M, Tice AD, Rustgi VK, Rodriguez-Torres M, Lurie Y, Cianciara J, Bacon BR, **Bain VG**, Kryczka W, Pulkstenis E, Subramanian GM, McHutchison JG,
Efficacy and safety of albinterferon alfa-2B in combination with ribavirin in treatment naive patients with chronic hepatitis C genotype 1
Hepatology, 50:4, 333A, 2009

152. Lambert J, **Bain VG**, Thomson AB, Clandinin MT,
Effectiveness of dietary intervention for liver post-transplant hyperlipidemia
Hepatology, 50:4, 573A, 2009

153. Montano-Loza AJ, **Bain VG**, Ma M, Mason AL
Incidence and risk factors associated with de novo autoimmune hepatitis after liver

transplantation
Hepatology, 50:4, 591A-592A, 2009

154. Benhamou Y, Nelson DR, Chuang W-L, Lawitz E, Flisiak R, Rasenack J, Kryczka W, Lee C-M, Rodriguez-Torres M, **Bain VG**, Schiff ER, Cho M, Janczewska-Kazek E, Peng C-Y, Pulkstenis E
Efficacy and safety results of albinterferon alfa-2B in combination with ribavirin in treatment naive subjects with chronic hepatitis C genotype 2 or 3
Hepatology, 50:4, 1026A, 2009

155. Montano-Loza A, Mason A, Ma M, **Bain VG**, Tandon P
Risk factors for recurrence of autoimmune hepatitis after liver transplantation
The Canadian Journal of Gastroenterology, 23:A, 77A, 2009

156. Ye C, Meghana Saincher M, Tandon P, Meeberg G, Burak KW, **Bain VG**.
Cardiac workup protocol for liver transplant candidates.
Hepatology, 52:4, 842A, 2010

157. Zeuzem S, Pianko S, Foster GR, **Bain V**, Chuang WL, Sarin SK, Flisiak R, Lee CM, Shah SR, Andreone P, Piratvisuth T, Yin Y, Feutren G, Jacobson IM.
Safety and efficacy of Albinterferon-Alfa-2B every four weeks plus ribavirin for treatment of chronic hepatitis C genotype 2/3.
Hepatology, 52:4, 81A, 2010

158. Montano-Loza AJ, **Bain VG**, Mason AL
Incidence and risk factors associated with de novo autoimmune hepatitis after liver Transplantation.
Canadian Journal of Gastroenterology, 24:A, 72A, 2010

159. Peltekian K, **Bain V**, Lee S, Sherman M, Cooper C, Yoshida E, Marotta P, Krajden M, Usaty C, Balshaw R, Deschenes M.
Is pre-treatment liver biopsy necessary in patients with chronic hepatitis C infections?
Canadian Journal of Gastroenterology, 24:A, 157A, 2010

160. Meza-Junco J, Montano-Loza A, Prado C, Lieffers J, Baracos V, **Bain V**, Spratlin J, Sawyer M.
Sarcopenia in Patients (pts) with Hepatocellular Carcinoma (HCC).
Journal of Clinical Oncology, 29: Suppl Abstract e14570

161. Zeuzem S, Pianko S, Foster G, **Bain V**, Chuang W, Sarin S, Flisiak R, Lee C, Shah S, Andreone P, Piratvisuth T, Yin Y, Feutren G, Jacobson M.
Safety and Efficacy of Albinterferon-alfa-2b Every four Weeks Plus Ribavirin for Treatment of Chronic Hepatitis C Genotype 2/3.
AASLD, HCV Clinical Trials Abstract, 2010

162. Brown K, Pianko S, Sarin SK, Jacobson I, Piratvisuth T, Shah S, Andreone P, Lee CM, Gould M, **Bain V**, et al., 2010

Decline in Pulmonary Physiology During Treatment of Chronic Hepatitis C with Long-Acting Interferon and Ribavirin.
Journal of Respiratory Critical Care Medicine, 183, A3040, 2010

163. Montano-Loza A, **Bain V**, Ma M, Mason A.
Incidence and Risk Factors Associated with De Novo Autoimmune Hepatitis After Liver Transplantation.
Canadian Journal of Gastroenterology, 24:A, 72A-73A, 2010

164. Tandon P, Ney M, Irwin I, Ma M, Gramlich L, **Bain V**, Baracos V, Montano-Loza A, Myers R.
Sarcopenia-An Objective Nutritional Assessment Tool that May Facilitate Prioritization of Liver Transplant Candidates.
Hepatology, AASLD Abstracts, 54:4 (Suppl), 665A, 2011

165. Chandok N, Mason A, Adams P, Ma M, **Bain V**, Marotta P, Montano-Loza A.
Assessment of the Optimal Dose of Azathioprine for Patients with Autoimmune Hepatitis.
Hepatology, AASLD Abstracts, 54 :4 (Suppl), 912A, 2011

166. Asthana S, Burak KW, Bailey J, Myers R, Meeberg G, Mason A, **Bain V**, Kneteman N.
Sirolimus-Based Immunosuppression is associated with Improved Sustained Virologic Response (SVR) to Antiviral Treatment for Patients with Recurrent Hepatitis C (HCV) Infection Post-Liver Transplant (LT)
Hepatology, AASLD Abstracts, 54 :4 (Suppl), 451A, 2011

167. Montano-Loza A, Meza-Junco J, Prado C, Lieffers J, **Bain V**, Sawyer M.
Sarcopenia Predicts Early Mortality in Patients with Cirrhosis
Canadian Journal of Gastroenterology, 25:A (Suppl), 73A, 2011

168. Myers R, Faris P, Shaheen A, Aspinall A, Meeberg G, Tandon P, Kneteman N, **Bain V**, Burak K.
Validation of the Five-Variable Model for End-Stage Liver Disease (5VMELD) for Predicting Mortality on the Liver Transplant Waiting List
Canadian Journal of Gastroenterology, 25:A (Suppl), 74A, 2011

169. Cembrowski GS, Tran DV, Higgins TN, Blakney G, **Bain VG**.
Evaluation of serial patient ALT and AST demonstrates 50% more biologic variability in AST : Another reason to stop ordering AST and ALT in tandem.
AACC Annual Meeting, 12-A-1150-AACC, 2012

170. Meza-Junco J, Montano-Loza A, Prado C, Lieffers J, Baracos V, **Bain V**, Sawyer M.
Sarcopenia in patients with hepatocellular carcinoma.
Canadian Journal of Gastroenterology, 26 :(SupplA) :89A, 2012

171. Nelson DR, Lawitz E, **Bain V**, Gitlin N, Hawkins T, Marotta P, Workowski K, Flamm S, Pang PS, McHutchison JG, McNally J, Urbanek P, Yoshida EM.

High SVR12 with 16 weeks of Tegobuvir and GS-9256 with Peginterferon-Alfa 2A and Ribavirin in treatment-naïve genotype 1 HCV patients.
Journal of Hepatology, 56:(Suppl 2), S6-S7, 2012

172. Montano-Loza A, Purdy D, **Bain V**, Meza-Junco J, Ma M, Wong W, Owen R.
Radioembolization with Yttrium-90 for Advanced Hepatocellular Carcinoma: A Canadian Experience.
Journal of Hepatology, 58: S263, 2013

173. Montano-Loza A, Meza-Junco J, Prado C, Tandon P, **Bain V**, Ma M, Beaumont C, Esfandiari N, Sawyer M, Baracos V.
New Cutoff Values for Sarcopenia for Predicting 6-month Mortality in Cirrhotic Patients.
Journal of Hepatology, 58: S221, 2013

174. Alghanem M, Mason A, **Bain V**, Ma M, Kneteman N, Burak K, Montano-Loza A.
Primary Sclerosing Cholangitis Recurs Earlier After Living Donor Liver Transplantation.
Hepatology58:(Suppl 4), 1014A, 2013

175. Selvarajah V, **Bain V**, Ma M, Bhanji R, Montano-Loza A.
Management of Autoimmune Hepatitis in Canada: A National Survey.
Canadian Journal of Gastroenterology, 27:(Suppl A), A180,2013

176. Montano-Loza A, Meza-Junco J, Baracos V, Tandon P, **Bain V**, Ma M, Beaumont C, Esfandiari N, Sawyer M, Kneteman N,
Muscle Wasting is Not Associated with Higher Mortality After Liver Transplantation.
Canadian Journal of Gastroenterology, 27:(Suppl A), A35,2013

177. Jayakumar S, Carbonneau M, Hotte N, Befus D, St. Laurent C, Owen R, McCarthy M, Madsen K, Bailey R, Ma M, **Bain V**, Rioux K, Tandon P.
Probiotics do not Reduce Portal Pressure in Patients with Decompensated Cirrhosis.
Canadian Journal of Gastroenterology, 27:(Suppl A), A31,2013

178.D'Souza P, Montano-Loza A, Halloran B, Teshima C, Zepeda-Gomez S, **Bain V**, Sultanian R, Sandha G.
A Novel Cholangioscopy-Assisted Clinical Subtyping System in Primary Sclerosing Cholangitis – The Edmonton Classification.
Canadian Journal of Gastroenterology, 28:(Suppl A), A61, 2014

179. Montano-Loza A, **Bain V**, Alghanem M, Kneteman N, Burak K.
Primary Sclerosing Cholangitis Recurs Earlier After Living Donor Transplant.
Canadian Journal of Gastroenterology, 28:(Suppl A), A34, 2014

180. Tandon P, Abraldes J, Keough A, Bastiampillai R, Jayakumar S, Carbonneau M, Wong E, Kao D, **Bain V**, Ma M.
The Effect of Antibiotics in Acute Variceal Hemorrhage: A Comparative Effectiveness Study.
Canadian Journal of Gastroenterology, 28:(Suppl A), A58, 2014

181. Bhanji R, Ma M, Bain V, Montano-Loza A.
Early Renal Dysfunction After Liver Transplantation is Associated with Reduced Graft and Patient Survival.
Journal of Hepatology, 60:(Suppl A), 873, 2014

182. Flamm S, Gane E, DuFour J-F, Rustgi V, **Bain V**, Crawford D, et al.
Safety of ABT-450/r/Ombitasvir + Dasabuvir With or Without Ribavirin in HCV Genotype 1-Infected Patients ≥65 Years of Age: Results From Phase 2 and 3 Trials.
Hepatology, 60:(Suppl A), 1157A, 2014

This is Exhibit "B" referred to in the
Affidavit of DR. VINCE BAIN
sworn (or affirmed) before me at
Edmonton, Alberta,
this 11 day of MARCH, 2015.

A Commissioner for the Province of ALBERTA

Yolanda Van Wachem
Barrister & Solicitor

SPECIAL ARTICLE

An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver

Robert P Myers MD MSc[1]*, Hemant Shah MD MScCH HPTE[2]*, Kelly W Burak MD MSc[1], Curtis Cooper MD[3], Jordan J Feld MD MPH[2]*

RP Myers, H Shah, KW Burak, C Cooper, JJ Feld. An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol Hepatol 2015;29(1):19-34.

Chronic hepatitis C remains a significant medical and economic burden in Canada, affecting nearly 1% of the population. Since the last Canadian consensus conference on the management of chronic hepatitis C, major advances have occurred that warrant a review of recommended management approaches for these patients. Specifically, direct-acting antiviral agents with dramatically improved rates of virological clearance compared with standard therapy have been developed and interferon-free, all-oral antiviral regimens have been approved. In light of this new evidence, an update to the 2012 Canadian Association for the Study of the Liver consensus guidelines on the management of hepatitis C was produced. The present document reviews the epidemiology of hepatitis C in Canada, preferred diagnostic testing approaches and recommendations for the treatment of chronically infected patients with the newly approved antiviral agents, including those who have previously failed peginterferon and ribavirin-based therapy. In addition, recommendations are made regarding approaches to reducing the burden of hepatitis C in Canada.

Key Words: *Dasabuvir; Direct-acting antivirals; Guideline; Hepatitis C; Interferon; Ledipasvir; Ombitasvir; Paritaprevir; Peginterferon; Simeprevir; Sofosbuvir; Ribavirin; Therapy; Treatment*

Mise à jour sur la prise en charge de l'hépatite C chronique : les lignes directrices consensuelles 2015 de l'Association canadienne pour l'étude du foie

L'hépatite C chronique demeure un fardeau médical et économique important au Canada, car il touche près de 1 % de la population. Depuis la dernière conférence consensuelle canadienne sur la prise en charge de l'hépatite C chronique, on a réalisé des progrès marqués qui justifient une analyse des démarches de prise en charge recommandées. Notamment, on a mis au point des antiviraux à action directe au taux de clairance virologique bien supérieur à celui du traitement standard et on a homologué des antiviraux sans interféron par voie orale. À la lumière de ces nouvelles données probantes, l'Association canadienne pour l'étude du foie a mis à jour les lignes directrices consensuelles 2012 sur la prise en charge de l'hépatite C. Le présent document traite de l'épidémiologie de l'hépatite C au Canada, des démarches et des recommandations favorisées pour traiter les patients atteints d'une infection chronique à l'aide des nouveaux antiviraux homologués, y compris les patients qui n'avaient pas répondu à un traitement à l'interféron pégylé et à la ribavirine. Il contient également des recommandations sur les approches pour réduire le fardeau de l'hépatite C au Canada.

The present guidelines were written to assist physicians and other health care professionals in the management of patients with chronic hepatitis C virus (HCV) infection. They were drafted by Canadian HCV experts at the request of the Executive Committee of the Canadian Association of the Study of the Liver (CASL). The document was made available for review by CASL members and a revised draft based on this feedback was submitted to the Executive Committee of CASL for approval. The information contained within the present guidelines represents a synthesis of evidence from the published literature and scientific abstract presentations available at the time of writing with supplementation by the expert opinions of the authors. Any recommendations should be considered preferred approaches to care rather than strict standards. In some cases, off-label use of regimens are recommended based on the authors' opinions. To more fully characterize the quality of evidence supporting these recommendations, we have assigned a class (reflecting benefit versus risk) and level (assessing strength of certainty) of evidence as adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (1,2), and as used in similar practice guidelines of CASL (3) and the American Association for the Study of Liver Diseases (4) (Table 1). No funding was provided to the authors for this work.

Since the last update of the CASL management guidelines for chronic hepatitis C (CHC) in 2012 (3), major advances have occurred including: the approval of novel direct-acting antiviral agents (DAAs) used with pegylated interferon (PEG-IFN) that have improved efficacy and tolerability compared with first-generation DAAs and/or standard PEG-IFN-based therapy (5-7); and the approval of all-oral, IFN-free, DAA combination therapies with markedly improved efficacy and tolerability and activity beyond just HCV genotype 1 (5,8-15). The current document was developed as an update to previous guidelines with a focus on the management of HCV-infected patients rather than an exhaustive review of CHC or HCV screening. Future guidelines will include 'special populations' with CHC, including people who use injection drugs (PWIDs), incarcerated individuals, patients with decompensated cirrhosis, those pre- or post-transplantation, and patients with HIV/HCV coinfection (for whom relevant guidelines have recently been published by the Canadian Institute of Health Research HIV Trials Network) (16). Due to the rapidity of advances in this field, recommendations in the present document will be updated regularly as new information emerges and novel agents are approved.

*Authors who contributed equally to this work.

[1]Liver Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta; [2]Toronto Western Hospital Liver Centre, University of Toronto, Toronto; [3]Division of Infectious Diseases, University of Ottawa, Ottawa, Ontario

Correspondence: Dr Robert P Myers, Liver Unit, University of Calgary, 6D22, Teaching, Research and Wellness Building, 3280 Hospital Drive Northwest, Calgary, Alberta T2N 4Z6. Telephone 403-592-5049, fax 403-592-5090, e-mail rpmyers@ucalgary.ca

Received for publication December 17, 2014. Accepted December 18, 2014

TABLE 1
Grading system for recommendations

Classification	Description
Class of evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure or treatment is beneficial, useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness/efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful
Grade of evidence	
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies or standard-of-care

EPIDEMIOLOGY OF HEPATITIS C IN CANADA

CHC remains a significant medical and economic burden in Canada (17-19). In the Canadian Health Measures Survey (20), Statistics Canada and the Public Health Agency of Canada reported an estimated anti-HCV prevalence of 0.5% (95% CI 0.3% to 0.9%) or approximately 138,600 (95% CI 55,800 to 221,300) anti-HCV-positive individuals in Canada. However, these figures are likely underestimates because the Canadian Health Measures Survey excluded several high-risk populations including incarcerated individuals, Aboriginals and PWIDs (20). In fact, a recent modelling study suggests that approximately 252,000 Canadians (uncertainty interval 178,000 to 315,000) were chronically infected in 2013 (18). The peak prevalence was estimated to have occurred in 2003, with approximately 260,000 infected individuals. It has been estimated that approximately 60% of HCV cases in Canada are among current or former PWIDs, 20% are among infected immigrants and 11% have received contaminated blood products (21). Of the nearly 8000 incident cases in Canada in 2007, approximately 80% likely occurred via sharing of injecting equipment, and most of the remainder among immigrants from endemic countries (21). There is wide variation in estimates of the number of HCV-infected individuals who remain undiagnosed. Modelling data from the Public Health Agency of Canada estimated that 79% of individuals were diagnosed in 2003 (21); however, the CMHS found that only 30% of anti-HCV-positive individuals were aware of their infection (20).

Genotype 1 infection is the most prevalent genotype in Canada, representing 65% of infected individuals (56% genotype 1a, 33% genotype 1b, and 10% with an unspecified subtype or mixed infection) (22). The genotype 1 subtype is of relevance for some of the new antiviral regimens due to differing efficacy between genotypes 1a and 1b. Genotypes 2 and 3 account for approximately 14% and 20% of infections in Canada, respectively, whereas genotypes 4, 5 and 6 are very rare (<1% of all infections) (22).

Although the overall prevalence of CHC is declining, complications of CHC are increasing due to aging of the infected population and progression of liver fibrosis (17-19). Modelling data suggest that by 2035, cases of decompensated cirrhosis, hepatocellular carcinoma (HCC) and liver-related mortality will increase by 80%, 205% and 160%, respectively, compared with 2013 levels (Figure 1) (18). Similarly, annual direct costs associated with CHC (excluding the cost of antiviral therapies) are expected to rise from an estimated $161 million in 2013 to >$258 million at the peak in 2032 (18). Given the alarming estimates of future disease burden, more accurate information regarding the incidence and prevalence of CHC and its sequelae is required to inform health care planning and the allocation of resources. The identification of undiagnosed cases and the dissemination of effective antiviral therapies should be prioritized to reduce complications of this disease (23).

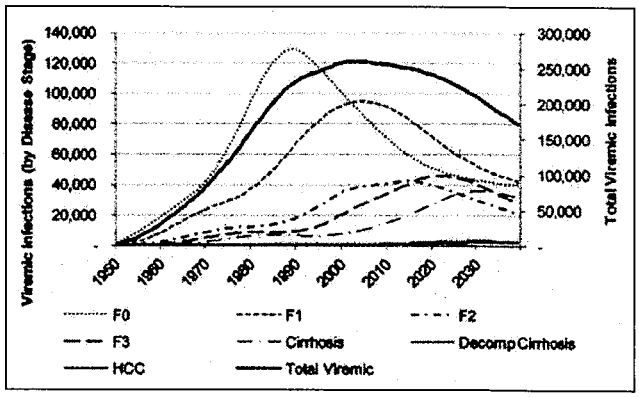


Figure 1) *Modelled incidence of hepatitis C-related sequelae in Canada, 1950 to 2035. Estimates are not mutually exclusive. Reproduced with permission from Myers et al (18). Decomp Decompensated; HCC Hepatocellular carcinoma*

Recommendations:

1. A large population-based seroprevalence survey should be conducted to accurately define the prevalence of hepatitis C in Canada. The design of the study should include populations with an increased risk of hepatitis C, particularly PWIDs, incarcerated individuals and immigrants from endemic countries (Class 2a, Level C).
2. To reduce the future burden of HCV-related morbidity and mortality in Canada, strategies for case identification, harm reduction and disease management – including but not limited to antiviral therapy – should be developed and implemented (Class 2a, Level C).

ANTIVIRAL THERAPY

The primary objective of anti-HCV therapy is complete eradication of the virus, termed a sustained virological response (SVR). SVR has traditionally been defined as undetectable serum HCV RNA at least 24 weeks following the end of treatment (SVR24) (24); however, recent data suggest that earlier assessment at 12 weeks after treatment (SVR12) is sufficient to define this outcome (25). Once achieved, an SVR is considered to be a long-term cure of the virus because late relapses are rare (26,27). SVR is associated with long-term health benefits including improved quality of life (28,29), extrahepatic manifestations of HCV (eg, cryoglobulinemic vasculitis) (30), liver histology (31,32), HCC incidence (33), liver-related morbidity and mortality (34-36), and all-cause mortality (33).

The landscape of antiviral treatment for hepatitis C is changing rapidly. Until recently, the standard therapy was the combination of PEG-IFN and ribavirin (RBV), usually administered for 48 weeks in patients with genotype 1, 4, 5 and 6, and 24 weeks in those with genotypes 2 and 3 (3). Dual therapy achieves SVR rates of 40% to 50% in patients with genotype 1 and approximately 80% in those with genotypes 2, 3, 5 and 6. Results for HCV genotype 4 are intermediate (3). In 2011, the first DAAs, boceprevir (BOC) and telaprevir (TVR), were approved for treatment of HCV genotype 1 in combination with PEG-IFN and RBV. These nonstructural (NS) 3/4A protease inhibitors (PIs) substantially increase rates of SVR in both treatment-naive and previously treated patients compared with dual therapy (37-41). However, they are associated with significant toxicity, complex regimens involving response-guided therapy (RGT), drug-drug interactions (DDIs), and low response rates in patients with cirrhosis and previous treatment failures. In addition, BOC and TVR required coadministration with PEG-IFN and RBV for 24 to 48 weeks, markedly increased the cost of therapy, and are associated with the emergence of resistance-associated variants (RAVs) in the majority of patients who fail treatment (3). The subsequent approval of DAAs with improved efficacy and tolerability, shorter treatment durations, and the option of PEG-IFN- and RBV-free therapy, represents a major advance in the field.

The treatment of CHC is complex and resource intensive. Contributing factors include the high prevalence of psychiatric comorbidities in HCV-infected individuals (eg, depression and addictions), multiple modes of drug administration, side effects, and the requirement for careful on-treatment monitoring of symptoms and laboratory tests. The most successful model to deliver comprehensive CHC care is via a multidisciplinary approach including experienced physicians, nurses and allied health professionals (eg, psychologists, psychiatrists, addiction specialists and social workers). Currently in Canada, a relatively small number of physicians treat CHC, leading in some cases to prolonged wait times for patients to be adequately evaluated and treated. These deficiencies in access to care are greater in rural and remote communities, despite a high HCV prevalence in many regions with limited health care capacity. Moreover, public funding for treatment nurses – who have represented a vital component of the management team – is not universally available. To achieve a meaningful reduction in the future burden of CHC, it will be vital to expand treatment capacity via additional training and funding of experienced personnel and enhanced access to publically funded antiviral therapies (42). With the advent of all-oral antiviral regimens that have few contraindications, minimal toxicity and short treatment courses, the number of patients that can be treated should increase dramatically. However, team-based management will still be necessary to achieve this goal.

Recommendation:

3. Increased resources are necessary to improve hepatitis C treatment capacity in Canada, including the training of expert treaters and public funding for treatment nurses (Class 2a, Level C).

INDICATIONS AND CONTRAINDICATIONS TO ANTIVIRAL TREATMENT

All patients with CHC should be considered candidates for antiviral treatment. The decision of if and when to initiate therapy should be based on the balance between the perceived benefits and risks of treatment and the wishes of the individual patient. Factors to consider include the probability of SVR and the likelihood of progression to advanced liver disease without viral eradication, the presence of extrahepatic manifestations of CHC, the patient's anticipated tolerability of treatment and the life expectancy of the patient. The prospect of new therapies with expected benefits over currently available treatments should also be considered. In light of these issues, prompt initiation of treatment should be considered in certain patient subgroups, especially those with advanced liver fibrosis (F3 or F4 according to the METAVIR classification [bridging fibrosis or cirrhosis]) (43). These patients are at the highest risk of HCV-related complications including liver failure and HCC. Treatment of patients with mild to moderate fibrosis (F1 or F2) should also be considered because progression to more advanced stages is associated with a reduced likelihood of SVR. Moreover, viral eradication in patients at risk of infecting others (eg, PWIDs who continue to share injecting equipment) may reduce the incidence of new infections (44). The curative nature of HCV therapy means that those who achieve SVR before developing cirrhosis do not require long-term follow-up. There are additional benefits to SVR beyond liver disease prevention, including improved quality of life (28,29) and a reduction in all-cause mortality (33). Patients with extrahepatic manifestations of CHC including cryoglobulinemic vasculitis, porphyria cutanea tarda and glomerulonephritis should be considered for treatment regardless of their underlying liver disease severity because these conditions typically respond to viral eradication (30).

TABLE 2
Contraindications for treatment with peginterferon and ribavirin

Absolute contraindications	Pregnancy
Strong, but not absolute, contraindications	Alcohol abuse
	Hepatic decompensation
	Coronary artery disease
	Solid organ transplantation (except liver)
Relative contraindications	Major depression
	Major psychosis
	Autoimmune disease
	Injection drug use
	Renal failure (including dialysis)
Contraindications that are no longer contraindications	Normal alanine aminotransferase
	Stable methadone maintenance
	Neutropenia, anemia or thrombocytopenia
	Controlled seizure disorder
	Older than 65 years of age
	Alcohol use

Table reproduced with permission from (3)

There are very few absolute contraindications to treatment with PEG-IFN- and RBV- based therapy. As postmarketing experience with these therapies has grown, many conditions previously regarded as absolute contraindications are now considered relative, and some may be present only temporarily (Table 2) (3). In most cases, treatment of these patients with PEG-IFN and RBV requires considerable expertise and, therefore, patients with relative contraindications should be treated in expert centres. Contraindications to the recently approved, all-oral regimens are distinctly uncommon.

Recommendations:

4. All patients with chronic HCV infection should be considered candidates for antiviral therapy (Class 1, Level A).
5. Antiviral treatment should be strongly considered in patients with evidence of liver fibrosis (Class 1, Level A).
6. Patients with extrahepatic manifestations of HCV should be considered for antiviral therapy (Class 1, Level A).

PRETREATMENT ASSESSMENT

Routine assessment

The routine assessment of HCV-infected patients should include risk factors for viral acquisition (eg, injection drug use, receipt of potentially contaminated blood products or tissues, and origin from a high-prevalence region), signs and symptoms of advanced liver disease (eg, jaundice, ascites, encephalopathy, portal hypertension-related hemorrhage) or extrahepatic manifestations of CHC, presence of cofactors that may accelerate disease progression (eg, alcohol use, obesity,

TABLE 3
Routine testing of patients with chronic hepatitis C virus (HCV)*

Category of Testing	Tests	Comments
Confirmation and characterization of chronic infection	HCV RNA	Confirms chronicity and baseline for treatment responses
	HCV genotype and subtype	Directs choice of treatment regimen
Assessment of liver disease	Complete blood count	Thrombocytopenia may indicate cirrhosis and portal hypertension. Platelets needed for APRI calculation
	Alanine aminotransferase	Normal value does not preclude significant fibrosis
	Asparatate amlnotransferase	Asparatate aminotransferase needed for calculation of APRI
	Gamma-glutamyl transferase	
	Alkallne phosphatase	
	Bilirubin	Elevated bilirubin or INR, or hypoalbuminemia may Indicate slgnificant liver dysfunction
	INR (or prothrombin tlme)	
	Albumin	
	Creatinine	Renal dysfunction increases ribavirin-related hemolytic anemia and may impact drug pharmacodynamics
	Abdomlnal ultrasound	May suggest cirrhosis, in which case, serves as a baseline for hepatocellular carcinoma surveillance
Viral coinfections	Immunoglobulin G anti-HAV	If negative, vaccinate against hepatitis A
	HBsAg	Exclude hepatitls B coinfection
	Hepatitis B surface antibody	If negative (and HBsAg-negative), vaccinate against hepatitis B
	anti-HIV	Exclude HIV coinfection
Exclude other causes of liver disease†	Alpha-1-antltrypsin	Alpha-1-antitrypsin deficiency
	Ceruloplasmin	Wilson disease.
	Ferritin, serum iron, total iron-binding capacity	Iron overload
	Antinuclear antibody	Autoimmune hepatitis
	Smooth muscle antibody	
	Antimitochrondrial antibody	Primary biliary cirrhosis
	Immunoglobulin G	Often elevated in autoimmune hepatitls and cirrhosis of any cause
	Immunoglobulin A	Often elevated in fatty liver and alcoholic llver disease
	Immunoglobulln M	Often elevated in prlmary biliary cirrhosis
Contraindications to treatment	Serurn or urine β-hurnan chorionic gonadotropin	Exclude pregnancy in women of reproductive age
	Electrocardiogram	If >50 years of age or history of cardlac disease
	Thyroid-stimulatlng hormone	Exclude thyroid disease, which may be exacerbated by interferon
	Fundoscopy	Exclude retinopathy in patients >50 years of age or with hypertension or diabetes mellitus If interferon is to be prescribed

**Confirmed anti-HCV antibody positive; †Suggested tests only. Tailor testing to individual case. Anti-HAV Antibodies to hepatitls A virus; APRI Aspartate aminotransferase/platelet ratio index; HBsAg Hepatitis B surface antigen; INR International normalized ratio*

coinfections) and potential contraindications to IFN-based therapy (Table 2), which would favour the use of an IFN-free regimen. Necessary laboratory testing includes virological tests to confirm and characterize HCV infection, liver biochemistry, abdominal ultrasound, an assessment of fibrosis stage and tests to rule out coinfections, direct appropriate vaccination and identify contraindications to treatment. In patients with abnormal liver biochemistry, serological tests to exclude coexisting liver diseases should be considered (Table 3).

Virological testing

Approximately one-quarter of patients infected with HCV will clear the virus spontaneously (45). Therefore, chronic HCV infection must be confirmed in all anti-HCV-positive individuals using a sensitive HCV RNA test. HCV RNA detection and quantification using real-time polymerase chain reaction assays is standard due to their sensitivity, specificity, accuracy and broad dynamic range. Results should be expressed in IU/mL and normalized to the WHO international standard. Quantitative assays with a lower limit of detection of approximately 10 IU/mL to 15 IU/mL are recommended. HCV RNA test results should be available within a timely fashion (within seven days) to facilitate management decisions. The rapid identification of failing treatment will reduce patient exposure to costly therapies and potential toxicity, and likely limit the development of RAVs.

The HCV genotype should be assessed in all patients because it has important implications for the decision to initiate treatment and the choice of regimen. With PEG-IFN and RBV therapy, knowledge of only the main genotype (1 to 6) was necessary. However, knowledge of the subtype is now critical, particularly for genotype 1, because of the differing genetic barriers to resistance of HCV subtypes 1a and 1b for many classes of DAAs (46,47). For some DAAs, additional testing (eg, for the Q80K polymorphism [see below]) and/or alternative treatment based on subtype (eg, the use of RBV) may be required.

Recommendations:

7. HCV RNA, genotype, and subtype testing (ie, 1a versus 1b) are essential to the management of patients with chronic hepatitis C (Class 1, Level A).
8. HCV RNA testing should be performed using a sensitive quantitative assay (lower limit of detection of ≤10 IU/mL to 15 IU/mL) with a broad dynamic range. Standardized results should be expressed in IU/mL and be available within a maximum of seven days to facilitate management decisions (Class 1, Level A).

Assessment of liver disease severity

Assessment of the severity of hepatic fibrosis is vital for determining the prognosis of HCV-infected patients and the necessity of antiviral treatment. Identification of patients with cirrhosis is particularly important due to their increased risk of hepatic complications, reduced

likelihood of treatment response, and their requirement for surveillance for HCC and esophageal varices. Although the diagnosis of cirrhosis is obvious in some cases based on routine tests (eg, a nodular shrunken liver, splenomegaly or portal hypertensive collaterals on ultrasound), traditionally, liver biopsy has been the reference method for staging fibrosis, determining the severity of other histological lesions (eg, necroinflammation, steatosis) and ruling out coexistent liver diseases (eg, iron overload). Various validated scoring systems have demonstrated sufficient reproducibility and interobserver variability to justify clinical use (eg, METAVIR, Scheuer, Ishak, and Knodell's Hepatic Activity Index) (48). However, liver biopsy has several limitations, including invasiveness and the potential for serious complications including hemorrhage (approximately one in 1000) and death (approximately one in 10,000) (49,50), sampling error and variability in pathological interpretation, high cost, limited availability in many centres, and the difficulty of repeating biopsies to monitor temporal changes in fibrosis. In light of these limitations, numerous noninvasive alternatives to biopsy have been developed (51) including serum markers (eg, the aspartate aminotransferase/platelet ratio index [52]), FibroTest (FibroSure, LabCorp, USA) (53), transient elastography (TE; FibroScan, Echosens, France) (54-57) and other imaging-based tools (58,59).

Although not universally available, a wealth of literature has confirmed that these noninvasive tools can be used instead of liver biopsy to stage HCV-related fibrosis at acceptable levels of accuracy and reproducibility. In a recent survey of Canadian specialists who manage patients with chronic liver disease (60), TE was the primary mode of fibrosis assessment in HCV-infected individuals in 53% of respondents, followed by liver biopsy in 37%. Nearly one-half of respondents estimated that these noninvasive alternatives have reduced their use of liver biopsy by over 50%. In general, these tests are highly accurate for diagnosing cirrhosis and have acceptable, but lower, performance for moderate to severe fibrosis (F2 or greater). The identification of mild fibrosis (F1) and the differentiation between individual stages is poor; however, these limitations also apply to liver biopsy. Emerging data have also demonstrated a correlation between these tests and HCV-related clinical outcomes (61-63), their cost-effectiveness compared with biopsy (64) and responsiveness to viral eradication (65,66). Future studies are necessary to determine the minimal clinically important changes in these markers to facilitate serial monitoring of fibrosis.

Recommendations:

9. Liver fibrosis assessment is vital to the management of patients with CHC (Class 1, Level A).
10. Acceptable methods of fibrosis assessment include liver biopsy, TE (FibroScan) and serum biomarker panels (eg, FibroTest), either alone or in combination. All jurisdictions should provide access to at least one accurate, noninvasive method to assess fibrosis (Class 1, Level A).
11. Alternatively, cirrhosis can be confidently diagnosed in some patients with clear clinical or radiographic evidence (Class 2a, Level C).

Utility of interleukin 28B testing

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene on chromosome 19 that are strongly associated with both spontaneous and treatment-induced HCV clearance (67-70). Patients with the favourable CC genotype at rs12979860 have a more than twofold likelihood of spontaneous HCV clearance compared with heterozygotes (CT) and homozygotes (TT) (67). The CC genotype is also associated with an approximately twofold increase in SVR to PEG-IFN and RBV therapy compared with the unfavourable SNPs in patients with HCV genotype 1 (68,70). The relevance in genotypes 2 and 3 and in treatment-experienced patients is less clear. There is marked ethnic variation in the prevalence of the IL28B genotypes.

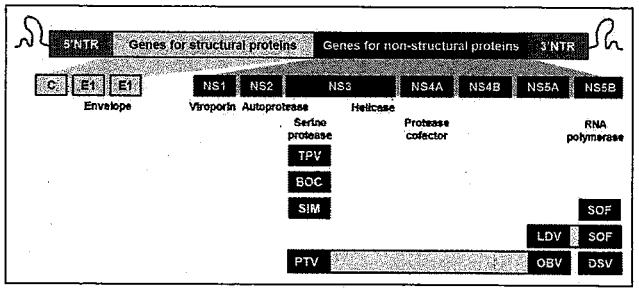


Figure 2) *Hepatitis C virus genome and the polyprotein targets of newly approved, direct-acting antiviral agents. Note: Sofosbuvir (SOF) is a nucleotide nonstructural protein (NS)5B polymerase inhibitor and dasabuvir (DSV) is a non-nucleoside polymerase inhibitor. BOC Boceprevir; LDV Ledipasvir; OBV Ombitasvir; PTV Paritaprevir; SIM Simeprevir; TPV Telaprevir*

The CC genotype is highly prevalent in Asians, but relatively uncommon in Africans, while Caucasians and Hispanics have an intermediate prevalence (68). Similar associations have been reported for the rs8099917 SNP (favourable allele = T and unfavourable allele = G) (71), and for the recently described IFN-lambda 4 (IFNL4) SNP ss46915590 (favourable allele = T and unfavourable allele = ΔG) (72). For simplicity, further discussion will refer to the rs12979860 SNP.

The impact of the IL28B genotype on treatment success is lower when treatment includes DAAs. Patients with the CC genotype have a very high rate of SVR when treated with DAAs plus PEG-IFN and RBV, reaching 98% with sofosbuvir (SOF)-based triple therapy for HCV genotype 1 (5). DAAs lead to a greater relative increase in SVR in non-CC patients. While the IL28B genotype is of limited importance with respect to SVR rates with IFN-free regimens (8,15), whether patients with the favourable IL28B genotype will be able to shorten therapy or use fewer DAAs is unclear.

Recommendations:

12. The IL28B genotype may provide valuable information regarding the likelihood of SVR depending on the HCV genotype and therapy under consideration (Class 2b, Level A).
13. A nonfavourable IL28B genotype does not preclude antiviral therapy (Class 1, Level A).

DAAs

Multiple steps in the HCV life cycle have proven attractive targets for novel pharmacological therapies (Figure 2). Particularly promising agents target the NS3/4A serine protease, the NS5B RNA-dependent RNA polymerase and the NS5A protein (73). The first DAAs approved by Health Canada for the treatment of HCV genotype 1 were the NS3/4A PIs, BOC and TVR. A second-generation PI, simeprevir (SIM), was approved in 2013 for use in combination with PEG-IFN and RBV for genotype 1. In 2013, the first HCV nucleotide polymerase inhibitor, SOF, was approved for use in combination with PEG-IFN and RBV for genotypes 1 and 4 and with RBV alone for genotypes 2 and 3. In 2014, the single-tablet regimen of SOF combined with the NS5A inhibitor ledipasvir (LDV) was approved for patients with HCV genotype 1, including those previously treated with BOC and TVR. In addition, the combination of the ritonavir-boosted PI paritaprevir (PTV_R), the NS5A inhibitor ombitasvir (OBV), and the non-nucleoside polymerase inhibitor dasabuvir (DSV) with or without RBV was approved for patients with HCV genotype 1. Given the markedly improved efficacy and tolerability of these regimens, all patients would benefit from IFN-free therapy. Therefore, these newly approved agents are recommended as first-line therapy for all indications throughout these guidelines. However, access to IFN-free regimens is not universal across Canada. Whether to initiate therapy with an IFN-containing regimen or wait for the availability of all-oral regimens is an individualized decision that must

consider the patient's wishes, the urgency of therapy, the severity of liver disease, the anticipated tolerability of PEG-IFN, the likelihood of SVR and the expected timeline for access to IFN-free regimens.

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPE 1 (TABLE 4)

PEG-IFN-free regimens

SOF/LDV: The nucleotide polymerase inhibitor SOF (400 mg) has been combined with the NS5A inhibitor LDV (90 mg) in a single tablet regimen (SOF/LDV) administered once daily. This combination was evaluated in treatment-naive patients in the open-label ION-1 (8) and ION-3 (10) phase 3 trials with a primary end point of SVR12. In the ION-1 study, which included patients with compensated cirrhosis (16%), participants were randomly assigned to 12 or 24 weeks of SOF/LDV with or without weight-based RBV (8). Among patients who received SOF/LDV for 12 weeks, SVR12 rates were 97% (211 of 217) and 99% (211 of 214) in those who received and did not receive RBV, respectively. In the 24-week treatment arms, SVR12 rates were 99% (215 of 217) in RBV-treated patients compared with 98% (212 of 217) in those who received SOF/LDV alone. There were no statistically significant differences between treatment arms or pretreatment characteristics that were predictive of response. Among the 136 cirrhotic patients, SVR12 rates ranged from 94% to 100%, with no differences between 12 and 24 weeks or with or without RBV. The IL28B genotype was not predictive of response; SVR12 rates ranged from 97% to 99% among patients with the unfavourable non-CC genotype. Only one patient experienced virological breakthrough on therapy and two patients relapsed. All three of these patients had NS5A resistance, but no SOF resistance was detected by deep sequencing. Although the majority of patients complained of at least one adverse event, 93% were mild to moderate in severity with the most common being fatigue, headache, insomnia and nausea. Adverse events were more common in patients randomized to receive RBV. No patient receiving SOF/LDV alone had a hemoglobin concentration <100 g/L.

In the ION-3 study (10), treatment-naive, noncirrhotic patients with HCV genotype 1 were randomly assigned to eight weeks of SOF/LDV with or without weight-based RBV, or SOF/LDV alone for 12 weeks. Among the 215 patients randomly assigned to SOF/LDV for eight weeks, 202 (94%) achieved SVR12, compared with 201 of 216 (93%) who received SOF/LDV/RBV for eight weeks, and 206 of 216 (95%) who received SOF/LDV for 12 weeks. The relapse rates were 5% (SOF/LDV) and 4% (SOF/LDV/RBV) in the eight-week treatment arms and 1% in the 12-week treatment arm. Although the 12-week regimen had a lower relapse rate, treating all patients for an additional four weeks would lead to overtreatment of the majority of individuals. Therefore, a post hoc analysis of baseline viral load was conducted to identify patients in whom an eight-week regimen would suffice (74). In this analysis, patients with an HCV RNA level <6 million IU/mL had a 2% relapse rate in both the eight-week (two of 123) and 12-week (two of 131) SOF/LDV treatment arms, and SVR12 rates of 97% (119 of 123) and 96% (126 of 131), respectively. However, in patients with a baseline viral load ≥6 million IU/mL, those treated for only eight weeks with SOF/LDV had a 10% (nine of 92) relapse rate versus only 1% (one of 85) if treated for 12 weeks. Corresponding SVR12 rates were 90% (83 of 92) and 94% (80 of 85), respectively. Based on these findings, Health Canada and the United States Food and Drug Administration (FDA) have recommended an eight-week regimen of SOF/LDV in treatment-naive, noncirrhotic patients with baseline HCV RNA <6 million IU/mL and 12 weeks in patients with a higher viral load (74).

In addition to baseline viral load, the impact of baseline RAVs on treatment response was examined (10). Although 15 of 23 relapsers (65%) to SOF/LDV had NS5A-resistant variants detected at the time of relapse (present at baseline in nine patients), SOF resistance was not identified. Among 116 patients (18%) with NS5A resistance at baseline, 90% achieved SVR12, suggesting a minimal impact of baseline NS5A RAVs on treatment response with SOF/LDV.

Recommendations:

14. In noncirrhotic, treatment-naive patients with HCV genotype 1, SOF/LDV should be given for eight weeks (Class 1, Level B).
15. In noncirrhotic, treatment-naive patients with genotype 1 and baseline HCV RNA ≥6 million IU/mL, extension of SOF/LDV therapy to 12 weeks can be considered (Class 1, Level C).
16. In cirrhotic, treatment-naive patients with genotype 1, SOF/LDV should be given for 12 weeks (Class 1, Level B).

PTV_R/OBV/DSV ± RBV: The PI PTV is given with low-dose ritonavir (PTV_R) to permit once-daily dosing. PTV_R (150 mg/100 mg) and the NS5A inhibitor OBV (25 mg) are coformulated in a single tablet taken as two tablets once daily. This tablet is combined with the nonnucleoside polymerase inhibitor DSV (250 mg) taken as one tablet twice daily. Placebo or the combination of the three DAAs plus ritonavir (referred to as the '3D' regimen) and weight-based RBV was given for 12 weeks to treatment-naive, noncirrhotic patients with HCV genotype 1 in the phase 3 SAPPHIRE-I trial (15). Patients randomly assigned to placebo subsequently received active treatment. Of 473 patients who started active therapy, 455 (96%) achieved SVR12, clearly superior to a historical control of TVR-based triple therapy in a similar patient population (estimated SVR12 of 78%). SVR12 did

TABLE 4
Treatment-naive patients with hepatitis C virus (HCV) genotype 1

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 1a, noncirrhotic	SOF/LDV × 8–12 weeks*	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24 weeks (if Q80K–)	PEG/RBV/BOC or TVR
				SIM/PEG/RBV × 24 weeks (if Q80K+)
Genotype 1b, noncirrhotic	SOF/LDV × 8–12 weeks*	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV × 12 weeks		SIM/PEG/RBV × 24 weeks	PEG/RBV/BOC or TVR
Genotype 1a, cirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24–48 weeks (if Q80K–)	PEG/RBV/BOC or TVR
				SIM/PEG/RBV × 24 weeks (if Q80K+)
Genotype 1b, cirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24 weeks	PEG/RBV/BOC or TVR

**In noncirrhotic, treatment-naive patients with HCV genotype 1a or 1b, treat with sofosbuvir/ledipasvir (SOF 400 mg/LDV 90 mg) once daily (one tablet) for eight weeks. Consider 12 weeks of treatment if baseline HCV RNA ≥6 million IU/mL. + Positive; – Negative; BOC Boceprevir; DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; Q80K Simeprevir-associated resistance variant at position 80; RBV Ribavirin (weight-based dosing: 1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg); SIM Simeprevir (150 mg once daily); SOF Sofosbuvir (400 mg once daily); TVR Telaprevir*

not differ between patients with HCV genotype 1a (95% [307 of 322]) or 1b (98% [148 of 151]). The only baseline factor associated with response was body mass index (BMI). Obese patients (BMI ≥30 kg/m^2) had an SVR12 rate of 91.5% compared with 97% in patients with a lower BMI. There was no difference in response according to IL28B genotype, fibrosis stage, baseline HCV RNA level, ethnicity or RBV dose modification.

Safety of the regimen was evaluated by comparing with patients randomly assigned to placebo (15). Adverse events were more common in those on active treatment (88%); however, 73% of placebo-treated patients also experienced at least one adverse event. Severe adverse events (2.1%), in particular those requiring drug discontinuation (<1%), were rare. The most common side effects were fatigue and headache, but were no more frequent with active treatment than placebo. Nausea, pruritus, insomnia, diarrhea and asthenia were reported more frequently in patients on active treatment. Total bilirubin elevations were seen in 2.8% of patients on this regimen, likely due to RBV-related hemolysis and inhibition of the bilirubin transporters OATP1B1 and OATP1B3 by PTV_R. No episodes of hepatotoxicity were reported. Grade 2 anemia (hemoglobin 80 g/L to 100 g/L) was reported in 5.8% of patients treated with this regimen including RBV. In 5.5% of patients, the RBV dose was modified due to adverse events, but no impact on the rate of SVR12 was observed in these patients.

The TURQUOISE-II phase 3 trial evaluated the PTV_R/OBV/DSV plus RBV regimen (12 versus 24 weeks) in treatment-naive and treatment-experienced patients with compensated cirrhosis (13). Among treatment-naive patients, the rates of SVR12 were similar between the 12- and 24-week arms (94% [81 of 86] versus 95% [70 of 74]) and by genotype subtype (genotype 1a: 12 versus 24 weeks: 92% [59 of 64] versus 93% [52 of 56]; and genotype 1b: 100% in both the 12-week [22 of 22] and 24-week [18 of 18] groups). SVR12 rates among previously treated patients from TURQUOISE-II are discussed below.

To evaluate the importance of RBV administration with PTV_R/OBV/DSV, the PEARL-III and PEARL-IV phase 3 trials were conducted in treatment-naive, noncirrhotic patients with genotypes 1b and 1a, respectively (75). In PEARL-III, patients with HCV genotype 1b were randomly assigned to receive PTV_R/OBV/DSV alone (n=209) or with RBV (n=210) for 12 weeks. Only three of 419 patients in the trial failed treatment; the SVR12 rate was 99% in both groups. In the PEARL-IV trial, of 205 patients with HCV genotype 1a randomly assigned to receive PTV_R/OBV/DSV alone for 12 weeks, 185 (90%) achieved SVR12; this rate was significantly lower than that observed in patients treated with PTV_R/OBV/DSV plus RBV (97% [97 of 100]), emphasizing the importance of RBV coadministration when this regimen is prescribed to patients with HCV genotype 1a (75).

Recommendations:

17. In treatment-naive patients with HCV genotype 1a infection, with or without cirrhosis, and for those with genotype 1b infection and cirrhosis, coformulated PTV_R/OBV/DSV should be given with weight-based RBV for 12 weeks (Class 1, Level A).
18. In noncirrhotic, treatment-naive patients with genotype 1b infection, coformulated PTV_R/OBV/DSV should be given without RBV for 12 weeks (Class 1, Level A).

SOF and SIM: SOF (400 mg daily) was combined with the second-generation PI SIM (150 mg daily) with or without RBV for 12 or 24 weeks in the phase 2 COSMOS study (76). The study was divided into two cohorts: cohort 1 included 80 null responders with mild fibrosis (F0 to F2) and cohort 2 included 87 treatment-naive and null responders with advanced fibrosis (F3 and F4). HCV RNA was suppressed on treatment in all patients, but six patients relapsed. The overall SVR12 rate was 92% (154 of 167), with similar results in cohorts 1 and 2 (90% [72 of 80] versus 94% [82 of 87], respectively). The SVR12 rates did not differ between 12 and 24 weeks of treatment, with or without RBV, or in treatment-naive versus treatment-experienced patients (95% [38 of 40] versus 91% [116 of 127]). The presence of a polymorphism at position 80 with a substitution of a K (lysine) for Q (glutamine), referred to as the 'Q80K' polymorphism, which is associated with reduced activity of SIM and found almost exclusively in patients with HCV genotype 1a (see below) (77,78), did not impact the rate of SVR12 (76). Although four of the six relapsers had genotype 1a infection and the Q80K polymorphism at baseline, 88% (51 of 58) of patients with this polymorphism still achieved SVR12. In this small trial, the regimen was well tolerated; headache, fatigue and nausea were the most commonly reported side effects. Only four patients (2%) discontinued treatment due to adverse events. Although the results from this trial are encouraging, given its small sample size and the availability of other effective and less expensive all-oral antiviral regimens, this regimen should be considered as a second-line option until further data emerge.

Recommendation:

19. In treatment-naive patients with HCV genotype 1a or 1b infection, with or without cirrhosis, SOF (400 mg daily) and SIM (150 mg daily) should be given for 12 weeks without RBV (Class 1, Level B).

PEG-IFN-containing regimens

Given the efficacy and markedly improved tolerability of SOF or SIM combined with PEG-IFN and RBV compared with TVR- or BOC-based regimens, the latter first-generation PIs should no longer be used except in rare circumstances where treatment is urgent and access to newer agents is not available. The use of BOC and TVR is reviewed in the 2012 version of the present guidelines (3).

SOF, PEG-IFN and RBV: SOF (400 mg daily) was combined with PEG-IFN and RBV for 12 weeks in patients with HCV genotypes 1, 4, 5 and 6 in the uncontrolled, open-label, phase 3 NEUTRINO trial (5). Among patients with HCV genotype 1, the SVR12 rate was 89% (261 of 292). Although a higher proportion of patients with genotype 1a achieved SVR12 than those with genotype 1b (92% [206 of 225] versus 82% [54 of 66]), this difference was not statistically significant. In multivariate analysis, the presence of cirrhosis and a non-CC IL28B genotype were the only predictors of virological failure. The SVR12 rate was 92% (252 of 273) in noncirrhotic patients versus 80% (43 of 54) in patients with compensated cirrhosis. The SVR12 rate was 98% (93 of 95) in patients with the IL28B CC genotype, compared with 87% (202 of 232) in those with a non-CC genotype. Although the side effect profile appeared similar to that of PEG-IFN and RBV dual therapy, the uncontrolled nature of the study precluded a clear evaluation of safety. However, only 2% of patients discontinued treatment due to an adverse event. Among the 28 patients who relapsed (9% of the cohort), resistance to SOF was not detected by deep sequencing (5).

Recommendation:

20. In patients with HCV genotype 1a or 1b, with or without cirrhosis, SOF (400 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks (Class 1, Level B).

SIM, PEG-IFN and RBV: In the QUEST-1 and QUEST-2 phase 3 trials (6,7), conducted in North America and Europe, respectively, the second-generation PI SIM (150 mg once daily) was combined with PEG-IFN and weight-based RBV for 12 weeks followed by an additional 12 or 36 weeks of PEG-IFN plus RBV and compared with PEG-IFN plus RBV for 48 weeks in patients with HCV genotype 1. Patients randomly assigned to triple therapy who had HCV RNA <25 IU/mL at week 4 and undetectable HCV RNA at week 12 continued PEG-IFN plus RBV for 12 additional weeks and then stopped all treatment. Patients who did not meet these early response criteria continued PEG-IFN and RBV for an additional 36 weeks (ie, 48 weeks total). In pooled data from these trials, the SVR12 rate in the SIM/PEG-IFN/RBV groups was 80% (419 of 521), significantly higher than in

patients receiving PEG-IFN and RBV alone (50% [132 of 264]) (6,7). In total, 88% (459 of 521) of patients in the SIM/PEG-IFN/RBV groups qualified for shortened therapy and 88% (405 of 459) of these patients achieved SVR12. In the two trials, of the 12% (62 of 521) of patients who did not qualify for shortened therapy, the SVR12 rate was 32% despite up to 36 weeks of additional PEG-IFN and RBV. SVR12 rates differed according to baseline fibrosis level, decreasing from 84% (317 of 378) in patients with F0 to F2 fibrosis to 60% (29 of 48) in those with cirrhosis. The IL28B genotype was also important, with SVR12 rates of 95% (144 of 152) in CC patients treated with triple therapy compared with 80% (63 of 79) with PEG-IFN and RBV alone, and 75% (275 of 369) in patients with a non-CC genotype who received triple therapy compared with 37% (69 of 185) in the control arm.

The most important predictor of response was the presence of the Q80K polymorphism at baseline (described above). In pooled data from these trials (6,7), the SVR12 rate with SIM-based triple therapy was 58% (49 of 84) in patients with genotype 1a and Q80K; no different than that seen in the PEG-IFN and RBV control arm (52% [23 of 44]). In contrast, among patients with genotype 1a infection without Q80K, the SVR12 rate was 84% (138 of 165), similar to that seen in patients with genotype 1b infection (85% [228 of 267]) and significantly higher than found in the control arms (43% [36 of 83] in genotype 1a without Q80K and 53% [70 of 133] in genotype 1b). In these trials, the Q80K polymorphism was present at baseline in 34% of patients with genotype 1a infection and available sequencing data, but in only one of 400 patients with genotype 1b (6,7). Rates of Q80K positivity among patients with HCV genotype 1a in Canada have been reported to be as high as 47% (79).

SIM was well tolerated in these trials (6,7). In pooled data across the SIM study program (80), the main adverse events seen more frequently in SIM-treated patients were rash (mostly mild) seen in 23% of patients (versus 17% of controls) and photosensitivity in 3.3% (versus 0.5% of controls). Total bilirubin elevation, which is due to inhibition of biliary transporters and RBV-related hemolytic anemia, was observed in 7.9% of patients (versus 2.8% of controls). Notably, the incidence of anemia was similar among patients treated with SIM-based triple therapy versus PEG-IFN and RBV alone.

Recommendations:

21. In patients with HCV genotype 1b infection and patients with genotype 1a infection without the Q80K polymorphism, SIM (150 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks followed by an additional 12 weeks of PEG-IFN plus RBV (Class 1, Level A).
22. Patients with genotype 1a infection must be tested for the Q80K polymorphism before starting therapy with SIM, PEG-IFN and RBV. Patients with the Q80K polymorphism should be treated with an alternative regimen (Class 1, Level A).
23. RGT should not be used with SIM, PEG-IFN and RBV. Patients who have HCV RNA ≥25 IU/mL at week 4 or detectable HCV RNA at week 12 should stop all therapy given the low probability of SVR and the need for prolonged exposure to PEG-IFN and RBV (Class 2b, Level C).

TREATMENT-EXPERIENCED PATIENTS WITH HCV GENOTYPE 1 (TABLE 5)

PEG-IFN-free regimens

Patients who have failed IFN-based therapy should be categorized as relapsers (undetectable HCV RNA during treatment with reappearance of HCV RNA within six months of stopping therapy), partial responders (decline of at least 2 $\log_{10}$ IU/mL in HCV RNA without ever achieving undetectable HCV RNA during therapy), or null responders (<2 $\log_{10}$ IU/mL decline in HCV RNA during therapy; or breakthrough [increase by >1 $\log_{10}$ IU/mL in HCV RNA above nadir despite ongoing antiviral therapy]) (3). Patients with an unknown previous response should be managed as null responders. As in treatment-naive patients, all previously treated patients with HCV genotype 1 would benefit from all-oral DAA regimens rather than those containing IFN because these patients, with the exception of relapsers, have demonstrated poor IFN responsiveness.

SOF/LDV: The single tablet regimen of SOF/LDV was evaluated in treatment-experienced patients in the ION-2 phase 3 trial (9). The study included relapsers (56%) and nonresponders (44%), including patients who had failed PEG-IFN/RBV dual therapy (48%) or in combination with a PI (52%). Patients were randomly assigned to receive 12 or 24 weeks of treatment with or without weight-based RBV. The SVR12 rate was 94% (102 of 109) in patients who received 12 weeks of SOF/LDV and 96% (107 of 111) in those who also received RBV. The SVR12 rate in patients who received 24 weeks of SOF/LDV therapy was 99% (218 of 220 overall) whether the patients also received RBV. Virological relapse occurred in 4% to 6% of patients treated for 12 weeks, but in none treated for 24 weeks. The SVR12 rate in patients with compensated cirrhosis (20% of each treatment arm) treated for 12 weeks with SOF/LDV alone was 86% (19 of 22) versus 82% (18 of 22) in those who also received RBV. In cirrhotic patients treated for 24 weeks (with or without RBV), the SVR12 rate was 100% (44 of 44). No baseline or on-treatment predictors of relapse were identified in patients with cirrhosis. There were no differences in SVR12 rates according to receipt of RBV, previous antiviral regimen (PEG-IFN/RBV versus PEG-IFN/RBV plus a PI), or previous treatment response (relapse versus nonresponse). Among the 62 patients (14%) with detectable NS5A resistance at baseline, 55 (89%) achieved an SVR12. All 11 patients who relapsed had detectable NS5A resistance at the time of relapse, but SOF-associated resistance was not detected. Among patients previously treated with a PI-containing regimen, 71% had NS3/4A resistance at baseline and 98% of these patients achieved an SVR12 (9). Tolerability of SOF/LDV was similar to that observed in the ION-1 and ION-3 studies (see above) (8,10); more adverse events were reported in patients treated with RBV.

Based on the higher rates of response observed in the ION-2 trial among previous treatment failure patients with compensated cirrhosis treated for 24 versus 12 weeks, Health Canada and the FDA have recommended a 24-week regimen of SOF/LDV in this patient subgroup. However, a subsequent and significantly larger randomized trial from France (the SIRIUS trial) (81) suggested that a 12-week regimen of SOF/LDV plus weight-based RBV is as effective as a 24-week SOF/LDV regimen in patients with cirrhosis who had failed both PEG-IFN/RBV and triple therapy including a PI. Specifically, 74 of 77 patients (96%) randomly assigned to SOF/LDV/RBV for 12 weeks had an SVR12 (4% relapse rate) compared with 75 of 77 patients (97%) randomly assigned to SOF/LDV alone for 24 weeks (3% relapse rate). Furthermore, in a pooled analysis of data from the SIRIUS trial and six other phase 2 and 3 studies that included 352 treatment-experienced patients with cirrhosis (82), 12 weeks of SOF/LDV/RBV resulted in a similar SVR12 rate to 24 weeks of SOF/LDV alone (96% versus 98%).

Recommendations:

24. In noncirrhotic patients with HCV genotype 1 who have failed previous therapy with PEG-IFN and RBV, with or without a PI, SOF/LDV without RBV should be given for 12 weeks (Class 1, Level B).
25. In cirrhotic patients with genotype 1 who have failed previous therapy with PEG-IFN and RBV, with or without a PI, SOF/LDV and weight-based RBV should be given for 12 weeks (Class 1, Level A).

PTV_R/OBV/DSV and RBV: The combination of PTV_R/OBV/DSV with weight-based RBV was evaluated in treatment-experienced patients without cirrhosis in the SAPPHIRE-II phase 3 trial (14). Among 297 patients randomly assigned to PTV_R/OBV/DSV plus RBV regimen for 12 weeks, 286 (96%) achieved SVR12. No pre- or on-treatment predictors of response were identified. The SVR12 rate was

TABLE 5
Treatment-experienced patients with hepatitis C virus (HCV) genotype 1

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 1a, noncirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks†	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks		SIM/PEG/RBV × 24–48 weeks (if Q80K–)†‡	PEG/RBV/BOC or TVR
				SIM/PEG/RBV (if Q80K+)
Genotype 1b, noncirrhotic	SOF/LDV × 12 weeks	SOF/SIM × 12 weeks†	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV × 12 weeks		SIM/PEG/RBV × 24–48 weeks†,‡	PEG/RBV/BOC or TVR
Genotype 1a, cirrhotic	SOF/LDV/RBV × 12 weeks	SOF/LDV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12–24 weeks*	SOF/SIM × 12 weeks†	SIM/PEG/RBV × 24–48 weeks (if Q80K–)†‡	PEG/RBV/BOC or TVR
				SIM/PEG/RBV if Q80K+)
Genotype 1b, cirrhotic	SOF/LDV/RBV × 12 weeks	SOF/LDV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	PTV_R/OBV/DSV/RBV × 12 weeks	SOF/SIM × 12 weeks†	SIM/PEG/RBV × 24–48 weeks†‡	PEG/RBV/BOC or TVR

**Patients with HCV genotype 1a, cirrhosis and previous null response should receive 24 weeks of PTV_R/OBV/DSV/RBV (paritaprevir/ritonavir/ombitasvir/dasabuvir/ribavirin) if treated with this regimen. Relapsers and partial responders with genotype 1 and cirrhosis can be treated for 12 weeks with PTV_R/OBV/DSV/RBV; †Simeprevir (SIM)-containing regimens should not be given to patients who have failed previous therapy with a protease inhibitor; ‡Previous null responders with genotype 1a or 1b should not be treated with SIM/ Peginterferon alfa-2a or peginterferon alfa-2b (PEG)/RBV regardless of the presence or absence of cirrhosis. Previous relapsers should be treated for 24 weeks total (12 weeks of SIM/PEG/RBV followed by 12 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at week 12. Otherwise, all treatment should be discontinued. Partial responders should be treated for 48 weeks total (12 weeks of SIM/PEG/RBV followed by 36 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at weeks 12 and 24; otherwise, all treatment should be discontinued. + Positive; – Negative; BOC Boceprevir; DSV: 250 mg one tablet twice daily; IFN Interferon; PEG: Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV: 150 mg/100 mg/25 mg, two tablets once daily; Q80K SIM-associated resistance variant at position 80; RBV weight-based dosing: 1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg; SIM: 150 mg once daily; SOF Sofosbuvir (400 mg once daily); SOF/LDV SOF 400 mg/ledipasvir 90 mg once daily (one tablet); TVR Telaprevir*

similar between patients with genotype 1a (96% [166 of 173]) and 1b (97% [119 of 123]), and did not differ between relapsers (95% [82 of 86]), partial responders (100% [65 of 65]) and null responders (95% [139 of 146]). RAVs to one or more of the three DAAs in the regimen were detected in five of the seven patients with post-treatment relapse (14).

In the TURQUOISE-II trial (13), PTV_R/OBV/DSV plus RBV regimen for 12 or 24 weeks was evaluated in 380 patients with compensated cirrhosis, of whom 58% had previously failed PEG-IFN and RBV therapy. Among patients with genotype 1b, the SVR12 rate was 99% (67 of 68) with 12 weeks of therapy and 100% (51 of 51) with 24 weeks. Response rates did not differ according to treatment duration or previous treatment history. In patients with genotype 1a infection, SVR12 rates were 89% (124 of 140) with 12 weeks and 94% (114 of 121) with 24 weeks of therapy; this difference was not statistically significant. There was no difference between the 12- and 24-week study arms among treatment-naive, cirrhotic patients with genotype 1a (12 versus 24 weeks: 92% [59 of 64] versus 93% [52 of 56]), previous relapsers (93% [14 of 15] versus 100% [13 of 13]) or partial responders (100% [11 of 11] versus 100% [10 of 10]). However, among null responders with genotype 1a, the 24-week arm was superior to 12 weeks of treatment (93% [39 of 42] versus 80% [40 of 50]) (13).

To determine the importance of RBV in noncirrhotic, treatment-experienced patients with HCV genotype 1b infection, the PEARL-II study randomly assigned patients to receive PTV_R/OBV/DSV with or without RBV for 12 weeks (83). All 91 patients (100%) who received PTV_R/OBV/DSV alone achieved SVR12 compared with 97% (85 of 88) randomly assigned to also receive RBV.

There is expected to be overlap between RAVs due to PI-based therapies. Because the PTV_R/OBV/DSV regimen contains a PI and other regimens with documented activity in these patients are available (ie, SOF/LDV) (9), this regimen should not be used in patients who have failed another PI (eg, TVR, BOC or SIM).

Recommendations:

26. In noncirrhotic, treatment-experienced patients with HCV genotype 1a infection, coformulated PTV_R/OBV/DSV should be given with weight-based RBV for 12 weeks (Class 1, Level A).
27. In noncirrhotic, treatment-experienced patients with genotype 1b infection, coformulated PTV_R/OBV/DSV should be given without RBV for 12 weeks (Class 1, Level A).
28. In cirrhotic patients with genotype 1a infection and a history of previous null response to PEG-IFN and RBV, coformulated PTV_R/OBV/DSV should be given with RBV for 24 weeks (Class 1, Level B).
29. In patients who have failed therapy with another PI, coformulated PTV_R/OBV/DSV should not be given due to the potential for cross-resistance with PTV (Class 2b, Level C).

SOF and SIM: As previously described, SOF (400 mg daily) was combined with the PI SIM (150 mg daily) with or without RBV for 12 or 24 weeks in the phase 2 COSMOS study (76). Cohort 1 included 80 null responders with mild fibrosis (F0 to F2) and cohort 2 included 47 null responders (plus 40 treatment-naive patients) with advanced fibrosis (F3 and F4). Overall, 116 of 127 null responders (91%) achieved an SVR12, not significantly different from that observed among treatment-naive subjects (95% [38 of 40]). SVR12 rates among null responders were similar regardless of fibrosis severity (F0 to F2: 90% [72 of 80] versus F3: 96% [23 of 24] versus F4: 91% [21 of 23]), treatment duration or receipt of RBV. Given the expected cross-resistance between other PIs and SIM, patients who previously failed treatment with these agents were excluded from the study (76). Because of the small sample size of this trial and the availability of other effective and less expensive IFN-free regimens, this combination should be considered as a second line option until further data emerge.

Recommendations:

30. In patients with HCV genotype 1a or 1b infection, with or without cirrhosis, who have failed previous therapy with PEG-IFN and RBV, SOF (400 mg daily) and SIM (150 mg daily) should be given without RBV for 12 weeks (Class 1, Level B).
31. The combination of SOF and SIM should not be used in patients who have failed therapy with another PI (Class 2b, Level C).

PEG-IFN-containing regimens

Given the efficacy and markedly improved safety and tolerability of SOF and SIM combined with PEG-IFN and RBV compared to TVR or BOC-based regimens, these first generation PIs should no longer be used except in rare circumstances (see above).

SOF, PEG-IFN and RBV: Experience with the use of SOF (400 mg) in combination with PEG-IFN and RBV in patients who have failed IFN-based therapy is limited. Nevertheless, Health Canada and the United States FDA have approved this regimen for treatment-experienced patients. Based on a modelling approach, the FDA projected an SVR12 rate of 78% in PEG-IFN and RBV treatment failures if retreated with SOF plus PEG-IFN/RBV for 12 weeks. In the NEUTRINO phase 3 trial of treatment-naive patients (5), 52 patients with HCV genotype 1 had characteristics typical of the treatment-experienced population (ie, advanced fibrosis [F3 and F4], a non-CC IL28B genotype and high baseline viral load [≥800,000 IU/mL]). Thirty-seven of these patients (71%) achieved SVR12 with 12 weeks of SOF/PEG-IFN/RBV (74). Although this regimen is also untested in patients who have failed therapy with a PI, the absence of cross-resistance between the PIs and SOF suggests that these patients should respond similarly to those who failed treatment with PEG-IFN/RBV alone.

Recommendation:

32. In patients with HCV genotype 1a or 1b infection, with or without cirrhosis, who have failed previous therapy with PEG-IFN and RBV with or without a PI, SOF (400 mg daily) should be given with PEG-IFN plus weight-based RBV for 12 weeks (Class 2b, Level C).

SIM, PEG-IFN and RBV: SIM (150 mg daily) has been evaluated in combination with PEG-IFN and weight-based RBV for 12 weeks followed by an additional 12 to 36 weeks of PEG-IFN and RBV in patients with HCV genotype 1 who failed IFN-based therapy in two trials. The phase 3 PROMISE study (84) included relapsers, whereas the phase 2b ASPIRE trial (85) also included partial and null responders. In the PROMISE trial (84), an RGT approach identical to that used in treatment-naive patients was evaluated (see above). Treatment with triple therapy was more effective than PEG-IFN and RBV dual therapy (SVR12: 79% [206 of 260] versus 36% [48 of 133]) in these relapsers. The majority of SIM-treated patients (93% [241 of 260]) were eligible to shorten treatment from 48 to 24 weeks and 83% of these patients (200 of 241) achieved SVR12. In patients with undetectable HCV RNA at week 4 (77% of the cohort), the SVR12 rate was 87% (173/200), compared with 60% in those with HCV RNA <25 IU/mL but detectable at week 4. Among patients who did not qualify for shortened therapy, the SVR12 rate was 40% (six of 15) despite 48 weeks of treatment. Of the 39 patients with compensated cirrhosis randomly assigned to triple therapy, 29 (74%) achieved SVR12 compared with five of 19 (26%) in the control arm. As reported in treatment-naive subjects from the QUEST-1 and QUEST-2 trials (6,7), patients with HCV genotype 1a and the Q80K mutation at baseline did not benefit from SIM treatment (SVR12 rates in the simeprevir and placebo arms: 47% [14 of 30] versus 30% [six of 20], respectively). RAVs similar to those selected by TVR and BOC emerged in most patients (90%) who did not achieve SVR12 in the SIM arm (84).

In the phase 2b ASPIRE trial (85), 462 patients who failed PEG-IFN/RBV therapy (40% relapsers, 35% partial responders and 25% null responders) were randomly assigned to receive SIM (100 mg or 150 mg or placebo) for 12, 24 or 48 weeks in combination with PEG-IFN and RBV for 48 weeks. In patients treated with SIM 150 mg daily for 12 weeks, SVR24 rates were 77% (20 of 26) in relapsers, 65% (15 of 23) in partial responders and 44% (eight of 18) in null responders; all superior to rates in the control arm (37%, 19% and 9%, respectively). Among null responders with cirrhosis (across all SIM 150 mg arms), 31% (four of 13) achieved SVR24 with SIM compared with neither of two patients treated with PEG-IFN and RBV.

Recommendations:

33. In patients with HCV genotype 1b or genotype 1a infection without the Q80K polymorphism who relapsed to PEG-IFN and RBV, SIM (150 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks followed by PEG-IFN plus RBV for an additional 12 weeks. All therapy should be discontinued in patients who have HCV RNA >25 IU/mL at week 4 or detectable HCV RNA at week 12 (Class 1, Level A).
34. In patients with previous partial or null response, alternative regimens should be considered given the low probability of SVR and the need for prolonged exposure to PEG-IFN and RBV with this regimen (Class 2b, Level B).

PATIENTS WITH HCV GENOTYPE 2 (TABLE 6)

SOF and RBV

In the phase 3 FISSION trial (5), SOF (400 mg daily) was administered in combination with weight-based RBV for 12 weeks to treatment-naive patients with HCV genotype 2. Patients randomly assigned to the control arm received a 24-week course of PEG-IFN and RBV (800 mg daily). Patients with cirrhosis accounted for approximately 20% of the study population. The SVR12 rates in the SOF/RBV and PEG-IFN/RBV arms were 97% (68 of 70) and 78% (52 of 67), respectively. The incidence of adverse events was consistently lower among patients who received SOF/RBV, particularly the influenza-like symptoms and depression characteristic of IFN-based therapy. In the phase 3 VALENCE trial (12), 32 treatment-naive patients with HCV genotype 2 received a 12-week regimen of SOF and weight-based RBV. As observed in the FISSION study (5), all but one of these patients (97%) achieved an SVR12. The response rate did not differ between cirrhotic (100% [two of two]) and noncirrhotic patients (97% [29 of 30]). In the phase 3 POSITRON trial (11), 143 IFN-ineligible patients with HCV genotype 2 were randomly assigned to receive SOF and weight-based RBV for 12 weeks or placebo. The majority of patients in this trial had contraindications to or refused IFN therapy; only 7% had previously

TABLE 6
Patients with hepatitis C virus genotype 2

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Treatment-naive	SOF/RBV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
			PEG/RBV × 24 weeks*	SOF/LDV
				PTV_R/OBV/DSV ± RBV
				SOF/SIM
Treatment-experienced, noncirrhotic	SOF/RBV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	PEG/RBV
Treatment-experienced, cirrhotic	SOF/PEG/RBV × 12 weeks	SOF/RBV × 16 weeks*	None	PEG/RBV/PI
				SOF/LDV
				PTV_R/OBV/DSV ± RBV
				SOF/SIM

**Clinically inferior regimen. DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PI Protease inhibitor (eg, boceprevir, telaprevir or simeprevir); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV Ribavirin (weight-based dosing [1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg] if combined with sofosbuvir (SOF); 800 mg daily if used in dual therapy with PEG); SIM Simeprevir (150 mg daily); SOF: 400 mg daily; SOF/LDV SOF 400 mg/ledipasvir 90 mg once daily (one tablet)*

failed IFN-based treatment. Among 109 patients with genotype 2 treated with SOF/RBV for 12 weeks, 101 patients (93%) achieved an SVR12, similar to results observed in the FISSION and VALENCE trials (5,12). SVR12 rates did not differ between patients with and without cirrhosis (94% [16 of 17] versus 92% [85 of 92]).

SOF (400 mg daily) and weight-based RBV has also been studied in treatment-experienced patients with HCV genotype 2 in the VALENCE (12) and FUSION (11) phase 3 trials. In VALENCE (12), 37 of 41 (90%) treatment-experienced patients had an SVR12 following a 12-week course of SOF/RBV. In the FUSION trial (11), 68 patients who had previously failed an IFN-containing regimen (approximately 75% due to relapse), were randomly assigned to receive SOF/RBV for either 12 or 16 weeks. Overall, an SVR12 was observed in 86% (31 of 36) of patients treated for 12 weeks versus 94% (30 of 32) treated for 16 weeks, although this difference was not statistically significant. In patients without cirrhosis, high rates of SVR12 were observed regardless of treatment duration (12 versus 16 weeks: 96% [25 of 26] versus 100% [23 of 23]). However, lower rates of response were observed among patients with cirrhosis (12 versus 16 weeks: 60% [six of 10] versus 78% [seven of nine]). Although this difference was not statistically significant, the poor response rate among patients treated for 12 weeks suggests that a 16-week regimen is preferred if SOF/RBV is prescribed to this patient subgroup, particularly in IFN-ineligible subjects. Tolerability of SOF/RBV was similar to that observed in the FISSION and POSITRON studies (5,11).

SOF, PEG-IFN and RBV

SOF, PEG-IFN, and weight-based RBV for 12 weeks has been studied in patients with HCV genotype 2 who failed previous therapy in an open-label phase 2 study (86). Among 23 patients with HCV genotype 2 (14 with cirrhosis), an SVR12 rate of 96% (22 of 23) was observed. High rates of response were observed among cirrhotic (93% [13 of 14]) and noncirrhotic patients (100% [nine of nine]). Among the entire study population (n=47), which also included 24 patients with genotype 3, three patients discontinued RBV due to anemia and one patient discontinued all therapy due to pain. Serious adverse events occurred in four patients (9%); the majority were considered due to PEG-IFN or RBV and none due to SOF.

Recommendations:

35. In treatment-naive patients with HCV genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).
36. In noncirrhotic, treatment-experienced patients with genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).
37. In IFN-eligible, treatment-experienced patients with genotype 2 and cirrhosis, SOF (400 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks. In IFN-ineligible patients, SOF (400 mg daily) should be given with weight-based RBV for 16 weeks (Class 1, Level B).

PATIENTS WITH HCV GENOTYPE 3 (TABLE 7)

SOF and RBV

In the phase 3 FISSION trial (5), SOF (400 mg daily) in combination with weight-based RBV for 12 weeks or PEG-IFN/RBV (800 mg daily) for 24 weeks were administered to 359 treatment-naive patients with HCV genotype 3. Overall, an SVR12 was observed in 56% (102 of 183) of patients randomly assigned to receive SOF/RBV compared with 63% (110 of 176) in those treated with PEG-IFN/RBV. This difference was not statistically significant. In light of the suboptimal responses observed with a 12-week SOF/RBV regimen in this trial, the VALENCE trial examined a 24-week course in patients with HCV genotype 3 (12). Among treatment-naive patients, 94% (99 of 105) achieved an SVR12; responses did not differ between cirrhotic (92% [12 of 13]) and noncirrhotic patients (95% [87 of 92]).

SOF/RBV combination therapy has also been studied in treatment-experienced patients with HCV genotype 3. In the FUSION phase 3 trial (11), 127 patients who had failed previous treatment were randomly assigned to 12 or 16 weeks of SOF and weight-based RBV. Overall, SVR12 rates were 30% (19 of 64) and 62% (39 of 63) in the 12- and 16-week groups, respectively. The presence of cirrhosis was a strong negative predictor of response in patients treated for 12 weeks; only 19% (five of 26) of cirrhotic patients and 37% (14 of 38) of noncirrhotic patients had an SVR12 with this regimen. In the 16-week treatment arm, SVR12 rates were 61% (14 of 23) among patients with cirrhosis and 63% (25 of 40) in those without cirrhosis. In this trial, the primary mode of treatment failure was relapse, which was observed among 66% (42 of 64) of patients treated for 12 weeks and 38% (24 of 63) of those treated for 16 weeks. Therefore, the VALENCE trial examined a longer course (24 weeks) of SOF/RBV therapy in 145 treatment-experienced patients with HCV genotype 3 (12). Among 98 noncirrhotic patients in this trial, an SVR12 was observed in 85 (87%). However, only 62% (29 of 47) of patients with cirrhosis had an SVR12. Based on these data, alternative treatment options are necessary in cirrhotic, treatment-experienced patients with HCV genotype 3.

SOF, PEG-IFN and RBV

SOF, PEG-IFN and weight-based RBV administered for 12 weeks was studied in patients with HCV genotype 3 who failed previous therapy in a small, open-label phase 2 study (86). Among 24 patients, 12 of whom had cirrhosis, an SVR12 rate of 83% (20 of 24) was observed. There was no difference in response between cirrhotic and noncirrhotic patients (83% [10 of 12] in both groups).

SOF/LDV plus RBV

The single tablet regimen of SOF/LDV has been studied in patients with HCV genotype 3 in the open-label, phase 2, ELECTRON-2 trial conducted in two centres in New Zealand (87). In this study, 51 treatment-naive patients (16% with cirrhosis) were randomly assigned to 12 weeks of SOF/LDV with or without weight-based RBV. Fifty treatment-experienced patients (44% with cirrhosis) all received SOF/LDV plus RBV. Among treatment-naive patients, SVR12 rates were 64% (16 of 25) in the SOF/LDV group and 100% (26 of 26) in those who received SOF/LDV plus RBV. In treatment-experienced patients

TABLE 7
Patients with hepatitis C virus genotype 3

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Treatment-naive, noncirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
			PEG/RBV × 24 weeks*	PTV_R/OBV/DSV ± RBV
				SOF/SIM
Treatment-naive, cirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
Treatment-experienced, noncirrhotic	SOF/RBV × 24 weeks	SOF/LDV/RBV × 12 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV/PI
Treatment-experienced, cirrhotic	SOF/PEG/RBV × 12 weeks	SOF/RBV × 24 weeks*	None	PTV_R/OBV/DSV ± RBV
		SOF/LDV/RBV × 12 weeks		SOF/SIM

**Approved, but clinically inferior regimen. DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PI Protease inhibitor (eg, boceprevir, telaprevir or simeprevir); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV Ribavirin (weight-based dosing [1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg] if combined with sofosbuvir (SOF); 800 mg daily if used in dual therapy with PEG); SIM Simeprevir (150 mg daily); SOF: 400 mg daily; SOF/LDV SOF (400 mg)/ledipasvir (90 mg) once daily (one tablet)*

treated with SOF/LDV/RBV for 12 weeks, noncirrhotic patients had higher SVR12 rates than those with cirrhosis (89% [25 of 28] versus 73% [16 of 22]). LDV has limited activity against genotype 3 HCV in vitro (88); therefore, although SOF/LDV is a potential therapeutic option in these patients, additional data in diverse populations are necessary before it can be recommended as first-line therapy over other SOF-containing regimens.

Recommendations:

38. In treatment-naive patients and noncirrhotic treatment-experienced patients with HCV genotype 3, SOF (400 mg daily) should be given with weight-based RBV for 24 weeks (Class 1, Level B).
39. In cirrhotic, treatment-experienced patients with HCV genotype 3, SOF (400 mg daily) should be given with PEG-IFN and weight-based RBV for 12 weeks (Class 1, Level B).

PATIENTS WITH HCV GENOTYPES 4, 5 AND 6 (TABLE 8)

There are limited data to guide treatment decision-making for patients with HCV genotypes 4, 5 or 6 due to the small numbers of patients enrolled in phase 3 clinical trials. In Canada, these genotypes are present in <1% of cases (22). Although the first-generation PIs, BOC and TVR, do not have clinically significant activity against genotypes 4, 5 or 6, SOF (5) and SIM (89) have activity against all of these genotypes. However, due to a paucity of published data, Health Canada and the United States FDA have approved only SOF for the treatment of HCV genotype 4.

PEG-IFN-free regimens

PTV_R/OBV ± RBV: The fixed-dose combination of the ritonavir-boosted, NS3/4A PI PTV_R and the NS5A inhibitor OBV was studied in patients with HCV genotype 4 in the PEARL-I study (90). Treatment-naive patients were randomly assigned to receive PTV_R/OBV with or without weight-based RBV for 12 weeks; all treatment-experienced patients received RBV. Nearly all patients (93%) in this study had mild fibrosis (F0 to F2) and none had cirrhosis. Among subjects who received PTV_R/OBV plus RBV, all treatment-naive (42 of 42) and treatment-experienced patients (41 of 41) achieved an SVR12. However, the SVR12 rate was lower (91% [40 of 44]) among treatment-naive patients randomly assigned to the RBV-free regimen, suggesting that RBV is necessary with this drug combination. The safety profile of PTV_R/OBV plus RBV was similar to that observed in patients with HCV genotype 1 who were also treated with DSV (14,15).

SOF/LDV: The single tablet regimen of SOF/LDV was evaluated in patients with HCV genotype 4 in a single-center, open-label phase 2a trial (National Institutes of Allergy and Infectious Diseases SYNERGY) (91). Twenty-one patients (38% treatment-experienced; 40% with cirrhosis) received SOF/LDV for 12 weeks. Among 20 patients who completed the post-treatment follow-up period, 19 (95%) achieved SVR12. No patient discontinued treatment due to an adverse event. In a similar, open-label study conducted among 25 patients with HCV genotype 6 (92% treatment-naive; 8% with cirrhosis; 80% IL28B CC genotype) from two centres (ELECTRON-2) (87), a 12-week regimen of SOF/LDV resulted in an SVR12 rate of 96% (24 of 25). Although in vitro data suggest that SOF/LDV should be efficacious in patients with HCV genotype 5 (88), it cannot currently be recommended in this patient subgroup until clinical trial data are available.

SOF and RBV: The all-oral combination of SOF (400 mg daily) and weight-based RBV for 12 or 24 weeks was studied in a randomized trial conducted among 103 Egyptian patients with HCV genotype 4 (52% treatment-experienced; 17% with compensated cirrhosis) (92). Among treatment-naive subjects, the SVR12 rates in the 12- and 24-week treatment arms were similar (84% [21 of 25] versus 92% [22 of 24]). Whereas noncirrhotic patients had similar responses in the 12- and 24-week treatment arms (86% [19 of 22] versus 90% [19 of 21]), patients with cirrhosis appeared to benefit from prolonged therapy (SVR12 in 12- versus 24-week arms: 67% [two of three] versus 100% [three of three]); however, the sample size was limited. Among treatment-experienced patients (41% nonresponders), a 24-week regimen was superior overall (SVR12 rates in 12- versus 24-week arms: 70% [19 of 27] versus 89% [24 of 27]) and in noncirrhotic patients (73% [16 of 22] versus 95% [20 of 21]). In patients with cirrhosis, SVR12 rates in the 12- and 24-week treatment groups were 60% (three of five) and 67% (four of six), respectively (92). These results were supported by a small trial of Egyptian persons living in the United States treated with SOF and weight-based RBV for 12 or 24 weeks (93). In treatment-naive patients, the SVR12 rate was 79% (11 of 14) in patients treated for 12 weeks and 100% (14 of 14) in those treated for 24 weeks. In treatment-experienced patients, corresponding SVR12 rates were 59% (10 of 17) and 87% (13 of 15).

PEG-IFN-containing regimens

SOF, PEG-IFN and RBV: In the phase 2 ATOMIC study (94), SOF (400 mg once daily) was administered for 24 weeks in combination with PEG-IFN/RBV to a small number of patients with HCV genotypes 4 and 6. SVR12 rates of 82% (nine of 11) in patients with genotype 4 and 100% (five of five) in genotype 6 were observed, supporting the antiviral activity of this regimen. In the phase 3 NEUTRINO study (5), a small subset of patients with HCV genotypes 4 (n=28), 5 (n=1) and 6 (n=5) received this regimen for a shorter 12-week treatment period, and SVR12 rates of 96% (27 of 28) in patients with genotype 4 and 100% (six of six) for genotypes 5 and 6 were reported. The one patient with genotype 4 who failed to achieve an SVR12 had cirrhosis and relapsed after cessation of therapy. The tolerability was similar to that observed historically among patients treated with PEG-IFN and RBV.

SIM, PEG-IFN and RBV: The RESTORE study was a phase 3, single-arm, open-label trial that evaluated SIM with PEG-IFN/RBV in 35 treatment-naive and 72 treatment-experienced patients with HCV genotype 4 (95). All patients received 12 weeks of triple therapy followed by 12 or 36 weeks of PEG-IFN and RBV dual therapy. Treatment-naive and relapser patients were eligible for RGT (an additional 12 weeks of PEG-IFN and RBV dual therapy if HCV RNA <25 IU/mL at week 4 and undetectable at week 12; otherwise, an additional 36 weeks) while partial and null responders received 36 weeks of dual therapy (48 weeks total). Overall, 65% (70 of 107) of patients achieved SVR12 (83% [29 of 35] of treatment-naive patients, 86% [19 of 22] of relapsers, 60% [six of 10] of partial responders and 40% [16 of 40] of null responders). The majority of patients (89% of treatment-naive and 91% of relapsers) met criteria for shortened therapy and SVR12 rates of 94% and 95% were observed in these groups, respectively. Safety was similar to that observed in other phase 3 trials of SIM/PEG-IFN/RBV therapy (6,7).

Recommendations:

40. Patients with HCV genotype 4 should be treated with coformulated PTV_R/OBV plus weight-based RBV or SOF/LDV alone for 12 weeks (Class 1, Level B).
41. Patients with HCV genotype 5 should be treated with SOF (400 mg daily) and PEG-IFN plus weight-based RBV for 12 weeks (Class 1, Level B).
42. Patients with HCV genotype 6 should be treated with SOF/LDV for 12 weeks (Class 1, Level B).

ANTIVIRAL RESISTANCE

Emergence of RAVs must be considered with all DAA-based therapies. Due to the high replication rate of HCV and the low fidelity of its RNA-dependent RNA polymerase, new variants emerge continuously (96-98). HCV circulates as a large of population of related viruses known as quasispecies. Variants with mutations that lead to DAA resistance emerge by chance and are present at low frequencies

TABLE 8
Patients with hepatitis C virus (HCV) genotypes 4, 5 and 6

Population	Recommended	Alternative (IFN-free)	Alternative (IFN-containing)	Not recommended
Genotype 4	PTV_R/OBV/RBV × 12 weeks	SOF/RBV × 24 weeks	SOF/PEG/RBV × 12 weeks	PEG/RBV
	SOF/LDV × 12 weeks		SIM/PEG/RBV × 24-48 weeks*	PEG/RBV/BOC or TVR
Genotype 5	SOF/PEG/RBV × 12 weeks	None	None	PTV_R/OBV/DSV ± RBV
Genotype 6	SOF/LDV × 12 weeks	None	SOF/PEG/RBV × 12 weeks	

**Treatment-naive and previous relapser patients with HCV genotype 4 should be treated for 24 weeks total (12 weeks of simeprevir/ peginterferon alfa-2a or peginterferon alfa-2b/ribavirin [SIM/PEG/RBV] followed by 12 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at week 12. Otherwise, all treatment should be discontinued. Partial and null responders with HCV genotype 4 should be treated for 48 weeks total (12 weeks of SIM/PEG/RBV followed by 36 weeks of PEG/RBV) if HCV RNA <25 IU/mL at week 4 and undetectable at weeks 12 and 24; otherwise, all treatment should be discontinued. BOC Boceprevir; DSV Dasabuvir (250 mg) one tablet twice daily; IFN Interferon; PEG Peginterferon alfa-2a (180 µg subcutaneously/week) or peginterferon alfa-2b (1.5 µg/kg/week); PTV_R/OBV Paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) two tablets once daily; RBV: weight-based dosing (1000 mg daily if <75 kg; 1200 mg daily if ≥75 kg); SIM: 150 mg once daily; SOF Sofosbuvir (400 mg once daily); SOF/LDV SOF(400 mg)/ledipasvir (90 mg) once daily (one tablet); TVR telaprevir*

before DAA exposure. With DAA exposure, these resistant variants have a selective advantage over wild-type virus and will emerge as the dominant strains in the quasispecies. The probability that resistance will emerge with particular DAAs depends on their genetic barrier to resistance. This barrier usually reflects the number of nucleotide substitutions that must occur for high-level resistance to emerge. For example, the common PI mutation, R155K, requires two substitutions in a genotype 1b virus, but a single substitution in a genotype 1a virus and, consequently, this variant is much more common in patients with genotype 1a (99). In addition to the genetic barrier, the fitness of the RAV is important. A RAV that replicates very poorly is unlikely to emerge on therapy and will be quickly suppressed by wild-type virus once selective drug pressure is removed (97,98). For example, the S282T variant that confers resistance to SOF has extremely low replicative fitness and, as a result, has been identified only rarely in patients during SOF therapy and quickly disappears on treatment cessation (100). In contrast, many variants resistant to NS5A inhibitors are very fit and compete well with wild-type virus (88,101). As a result, NS5A-resistant variants are found in 10% to 15% of genotype 1 patients before drug exposure and persist long after therapy is discontinued in patients who fail an NS5A inhibitor-containing regimen (8,9).

Strategies to overcome resistance include avoiding DAA monotherapy and DAA dose reductions, maximizing adherence, combining DAAs with nonoverlapping resistance profiles, choosing DAAs with high barriers to resistance, and combining DAAs with PEG-IFN and RBV (96). NS5A inhibitors (eg, LDV, OBV), non-nucleoside polymerase inhibitors (eg, DSV) and NS3/4A PIs (eg, TVR, BOC, SIM) have low barriers to resistance (88). However, when potent agents of multiple classes are combined, on-treatment virological failure is extremely rare (eg, one patient of 473 treated with PTV_R/OBV/DSV plus RBV in the SAPPHIRE-I trial) and post-treatment relapse is very uncommon (eg, seven of 463 patients in this trial) (15). However, resistance to two or all three classes of drugs has been identified in almost all patients with virological failure on this combination. LDV-resistant variants are also uncommon, but present at the time of relapse in most patients who fail SOF/LDV combination therapy (8,9).

There are no data to support pretreatment resistance testing. In patients who have failed a DAA-containing regimen, it is reasonable to assume that resistance to that DAA is present at the time of retreatment. Therefore, a regimen containing DAAs without overlapping resistance should be selected in this situation. For example, in patients who have failed TVR or BOC, SOF/LDV combination therapy is very effective. In the ION-2 trial (9), 159 of 163 patients (98%) with persistent PI resistance at treatment initiation achieved an SVR12 with this regimen. Although RAVs may return to pretreatment levels after prolonged duration off therapy, there are no data on treating patients with PI resistance with a PI-containing regimen (eg, PTV_R/OBV/DSV). Therefore, this approach should not be adopted, particularly given the presence of other proven alternatives (ie, SOF/LDV).

NS5A resistance is of slightly more concern because NS5A inhibitors are a component of most all-oral regimens (88). In patients with baseline NS5A resistance, 90% achieved SVR12 with SOF/LDV in the ION-1 (8) and ION-3 (10) trials. Although this SVR rate was slightly lower than in patients without baseline resistance, the differences were not statistically significant and, therefore, pretreatment identification of resistance would not change management. Detailed baseline sequencing was not performed on all patients treated with the PTV_R/OBV/DSV regimen in the phase 3 trials (13-15,75,83); however, the rates of virological failure were low, suggesting that baseline NS5A resistance is unlikely to be a major issue. Whether retreatment of patients with emergent NS5A resistance with an NS5A-inhibitor-containing regimen will be effective remains to be determined.

Recommendations:

43. DAAs should not be used as monotherapy (Class 1, Level B).
44. Dosage reductions of DAAs should not be used to manage treatment-related side effects (Class 2a, Level C).
45. Adherence with DAAs should be maximized to reduce the likelihood of resistance (Class 2a, Level C).
46. Patients who failed therapy with a PI in the past should be treated with a regimen that does not contain a PI (Class 1, Level B).
47. With the exception of testing for Q80K in patients being considered for treatment with SIM, PEG-IFN and RBV, there is no role for baseline resistance testing with current DAA regimens (Class 1, Level A).

DDIs

Before the initiation of any DAA, potential DDIs must be considered, including those attributable to prescription and over-the-counter pharmaceuticals and herbal preparations. Identification of potential interactions requires knowledge of the metabolism of these agents. All currently available HCV PIs (TVR, BOC, SIM, PTV) are inhibitors and substrates of Cytochrome P450 3A4 (CYP3A4). Ritonavir, which is used to increase exposure and allow for once-daily dosing of PTV, is also an inhibitor and substrate of CYP3A4. Therefore, PIs are contraindicated with medications that are potent inducers of CYP3A4/5, which would reduce plasma concentrations and the therapeutic effect of the PI, and for those highly dependent on CYP3A4/5 for clearance, in which elevated plasma concentrations are associated with serious and/or life-threatening events (ie, a narrow therapeutic index). Other drug-metabolizing pathways are involved in individual PI handling that may affect DDIs. NS5A inhibitors and nucleotide polymerase inhibitors have fewer known DDIs than PIs; however, before starting therapy, all concomitant medications should be reviewed. Reference to an online updated database of DDIs is recommended before starting therapy (eg, http://www.hep-druginteractions.org).

Recommendation:

48. All prescription, over-the-counter and herbal medications should be reviewed for possible interactions with DAAs before starting therapy (Class 1, Level C).

FUTURE THERAPEUTIC OPTIONS

Numerous additional antiviral agents are under investigation in various stages of clinical development, from phase 1 though premarketing approval. Promising DAAs include NS3/4A PIs (eg, asunaprevir, grazoprevir, sovaprevir, vedroprevir), NS5A inhibitors (eg, daclatasvir, GS-5816, elbasvir, ACH-3102 and samatasvir), and non-nucleoside (eg, beclabuvir and GS-9669) and nucleotide NS5B polymerase inhibitors (eg, MK-3682 and ACH-3422). As new data regarding these agents emerge, including their receipt of regulatory approval, these HCV management guidelines will be updated.

ACKNOWLEDGEMENTS: The authors would like to acknowledge members of the CASL Executive and CASL membership, particularly Drs Eberhard Renner, Rick Schreiber, Gisela Macphail, and Jerome Simon for helpful comments regarding this manuscript.

DISCLOSURES: Production of these guidelines was not supported by any third party. The authors report the following potential conflicts of interest: Dr Kelly Burak: Consulting fees from Astellas, Gilead Sciences, Janssen and Novartis. Speaking fees from Astellas. Research support from Bayer, Bristol-Myers Squibb and Oncozyme. Dr Curtis Cooper: Consulting fees from AbbVie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, Roche Canada and Vertex. Speaking fees from AbbVie, Boehringer-Ingelheim, Gilead Sciences, Janssen and Roche Canada. Research support from AbbVie, Gilead Sciences and Vertex. Dr Jordan Feld: Consulting fees from AbbVie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and Theravance. Research support from AbbVie, Boehringer-Ingelheim, Gilead Sciences, Janssen and Merck. Dr Robert Myers: Consulting fees from AbbVie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Roche Canada and Vertex. Speaking fees from AbbVie, Boehringer-Ingelheim, Gilead Sciences, Janssen, Roche Canada and Vertex. Research support from Gilead Sciences and Vertex. Dr Hemant Shah: Consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen and Merck. Speaking fees from AbbVie, Gilead Sciences, Janssen, Merck, Roche Canada and Vertex. Grant support from Boehringer-Ingelheim and Janssen.

REFERENCES

1. Shiffman RN, Shekelle P, Overhage JM, et al. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003;139:493-8.
2. American Heart Association. <http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf> (Accessed February 1, 2012).
3. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol 2012;26:359-75.
4. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:1433-44.
5. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
6. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014;384:414-26.
7. Jacobson IM, Dore GJ, Foster GR, et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): A phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014;384:403-13.
8. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889-98.
9. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483-93.
10. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879-88.
11. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867-77.
12. Zeuzem S, Dusheiko GM, Salupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993-2001.
13. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973-82.
14. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604-14.
15. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594-603.
16. Hull M, Shafran S, Tseng A, et al. CIHR Canadian HIV Trials Network Co-Infection and Concurrent Diseases Core: Updated Canadian adult guidelines for the treatment of hepatitis C infection in HIV-hepatitis C coinfected patients. Can J Infect Dis Med Microbiol 2014;25:311-20.
17. Myers RP, Liu M, Shaheen AA. The burden of hepatitis C virus infection is growing: A Canadian population-based study of hospitalizations from 1994 to 2004. Can J Gastroenterol 2008;22:381-7.
18. 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;28:243-50.
19. Schanzer DL, Paquette D, Lix LM. Historical trends and projected hospital admissions for chronic hepatitis C infection in Canada: A birth cohort analysis. CMAJ 2014;Open 2:E139-144.
20. Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. Health Rep 2013;24:3-13.
21. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007. Final Report. <http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf>. (Accessed February 1, 2012).
22. Antonishyn NA, Ast VM, McDonald RR, et al. Rapid genotyping of hepatitis C virus by primer-specific extension analysis. J Clin Microbiol 2005;43:5158-63.
23. Shah HA, Heathcote J, Feld JJ. A Canadian screening program for hepatitis C: Is now the time? CMAJ 2013;185:1325-8.
24. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: A cure and so much more. Clin Infect Dis 2011;52:889-900.
25. Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology 2014 [Epub ahead of print].
26. Maylin S, Martinot-Peignoux M, Moucari R, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology 2008;135:821-9.
27. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010;139:1593-601.
28. Myers RP, Cooper C, Sherman M, et al. Outcomes of chronic hepatitis C therapy in patients treated in community versus academic centres in Canada: Final results of APPROACH (a prospective study of peginterferon alfa-2a and ribavirin at academic and community centres in Canada). Can J Gastroenterol 2011;25:503-10.
29. Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis 1999;(19 Suppl 1):77-85.
30. Cacoub P, Ratziu V, Myers RP, et al. Impact of treatment on extra hepatic manifestations in patients with chronic hepatitis C. J Hepatol 2002;36:812-8.
31. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-13.
32. Poynard T, McHutchison J, Davis GL, et al. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. Hepatology 2000;32:1131-7.

33. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-93.
34. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-84.
35. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509-516, e501.
36. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8, e281.
37. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-16.
38. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med 2011;365:1014-24.
39. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-28.
40. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-206.
41. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1207-17.
42. MacParland SA, Bilodeau M, Grebely J, et al. The 3rd Canadian Symposium on Hepatitis C Virus: Expanding care in the interferon-free era. Can J Gastroenterol Hepatol 2014;28:481-7.
43. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20:15-20.
44. Hellard M, Rolls DA, Sacks-Davis R, et al. The impact of injecting networks on hepatitis C transmission and treatment in people who inject drugs. Hepatology 2014;60:1861-70.
45. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: A systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
46. Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology 2007;132:1767-77.
47. Sherman KE, Sulkowski MS, Zoulim F, et al. Follow-up of SVR durability and viral resistance in patients with chronic hepatitis C treated with telaprevir-based regimens: Interim analysis of the EXTEND study (Abstract 248). Hepatology 2011;54(Suppl 4):485A.
48. Bedossa P. Liver biopsy. Gastroenterol Clin Biol 2008;32:4-7.
49. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: A population-based study including 4275 biopsies. Liver Int 2008;28:705-12.
50. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49:1017-44.
51. Guha IN, Myers RP, Patel K, Talwalkar JA. Biomarkers of liver fibrosis: What lies beneath the receiver operating characteristic curve? Hepatology 2011;54:1454-62.
52. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: A systematic review. Hepatology 2007;46:912-21.
53. Poynard T, Imbert-Bismut F, Munteanu M, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV FibroSure) and necrosis (ActiTest) in patients with chronic hepatitis C. Comp Hepatol 2004;3:8.
54. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. Gastroenterology 2008;134:960-974.
55. Myers RP, Elkashab M, Ma M, Crotty P, Pomier-Layrargues G. Transient elastography for the noninvasive assessment of liver fibrosis: A multicentre Canadian study. Can J Gastroenterol 24:661-70.
56. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology 2012;55:199-208.
57. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat 2009;16:300-14.
58. Venkatesh SK, Ehman RL. Magnetic resonance elastography of liver. Magn Reson Imaging Clin N Am 2014;22:433-46.
59. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: A pilot study. Hepatology 2012;56:2125-33.
60. Sebastiani G, Ghali P, Wong P, et al. Physicians' practices for diagnosing liver fibrosis in chronic liver diseases: A nationwide Canadian survey. Can J Gastroenterol Hepatol 2014;28:23-30.
61. Vergniol J, Foucher J, Terrebonne E, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology 2011;140:1970-9, e1971-3.
62. Vergniol J, Boursier J, Coutzac C, et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology 2014;60:65-76.
63. Pang JX, Zimmer S, Niu S, et al. Liver stiffness by transient elastography predicts liver-related complications and mortality in patients with chronic liver disease. PLoS One 2014;9:e95776.
64. Steadman R, Myers RP, Leggett L, et al. A health technology assessment of transient elastography in adult liver disease. Can J Gastroenterol 2013;27:149-58.
65. Poynard T, Ngo Y, Munteanu M, et al. Biomarkers of liver injury for hepatitis clinical trials: A meta-analysis of longitudinal studies. Antivir Ther 2010;15:617-31.
66. Vergniol J, Foucher J, Castera L, et al. Changes of non-invasive markers and FibroScan values during HCV treatment. J Viral Hepat 2009;16:132-40.
67. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:798-801.
68. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
69. Kurbanov F, Abdel-Hamid M, Latanich R, et al. Genetic polymorphism in IL28B is associated with spontaneous clearance of hepatitis C virus genotype 4 infection in an Egyptian cohort. J Infect Dis 2011;204:1391-4.
70. Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105-9.
71. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat Genet 2009;41:1100-4.
72. Prokunina-Olsson L, Muchmore B, Tang W, et al. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nat Genet 2013;45:164-71.
73. Kronenberger B, Zeuzem S. New developments in HCV therapy. J Viral Hepat 2012;19(Suppl 1):48-51.
74. Gilead Sciences Inc. Product Monograph: Harvoni (Ledipasvir/Sofosbuvir) Tablets 90 mg/400 mg Antiviral Agent. <www.gilead.ca/pdf/ca/harvoni_pm_english.pdf>. October 14, 2014. (Accessed November 6, 2014).
75. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983-92.
76. Lawitz E, Sulkowski MS, Ghalib R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: The COSMOS randomised study. Lancet 2014;384:1756-65.
77. Bae A, Sun SC, Qi X, et al. Susceptibility of treatment-naive hepatitis C virus (HCV) clinical isolates to HCV protease inhibitors. Antimicrob Agents Chemother 2010;54:5288-97.
78. Paolucci S, Fiorina L, Piralla A, et al. Naturally occurring mutations to HCV protease inhibitors in treatment-naive patients. Virol J 2012;9:245.
79. Andonov A, Kadkhoda K, Osiowy C, Kaita K. Pretreatment resistance to hepatitis C virus protease inhibitors boceprevir/telaprevir in hepatitis C virus subgenotype 1a-infected patients from Manitoba. Can J Gastroenterol 2013;27:414-6.
80. Antiviral Drugs Advisory Committee Meeting Briefing Document. Simeprevir (TMC435) Treatment of Patients with Chronic Hepatitis C. NDA 205123. October 24, 2013. <www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM371624.pdf>. (Accessed November 17, 2014).

81. Bourliere M, Bronowicki JP, De Ledinghen V, et al. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy (Abstract LB-6). Hepatology 2014;60:13-4.
82. Bourliere M, Sulkowski M, Omata M, et al. An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with ledipasvir/sofosbuvir with or without ribavirin (Abstract 82). Hepatology 2014;60:239A.
83. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359-65, e351.
84. Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: A phase 3 trial. Gastroenterology 2014;146:1669-79, e1663.
85. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology 2014;146:430-41, e436.
86. Lawitz E, Poordad F, Brainard DM, et al. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. Hepatology 2014 [Epub ahead of print].
87. Gane EJ, Hyland RH, An D, et al. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection (Abstract LB-11). Hepatology 2014;60:22.
88. Gao M. Antiviral activity and resistance of HCV NS5A replication complex inhibitors. Curr Opin Virol 2013;3:514-20.
89. Moreno C, Berg T, Tanwandee T, et al. Antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2-6: TMC435-C202, a phase IIa, open-label study. J Hepatol 2012;56:1247-53.
90. Pol S, Reddy KR, Baykal T, et al. Interferon-free regimens of ombitasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results (Abstract 1928). Hepatology 2014;60:1129A.
91. Kapoor R, Kohli A, Sidharthan S, et al. All oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: Interim results from the NIAID SYNERGY Trial (Abstract 240). Hepatology 2014;60:321A.
92. Esmat GE, Shiha G, Omar RF, et al. Sofosbuvir plus ribavirin in the treatment of Egyptian patients with chronic genotype 4 HCV infection (Abstract 959). Hepatology 2014;60:662A-663A.
93. Ruane PJ, Ain D, Stryker R, et al. Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry. J Hepatol [Epub ahead of print].
94. Kowdley KV, Lawitz E, Crespo I, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): An open-label, randomised, multicentre phase 2 trial. Lancet 2013;381:2100-7.
95. Moreno C, Hezode C, Marcellin P, et al. Once-daily simeprevir (TMC435) with peginterferon/ribavirin in treatment-naive or treatment-experienced chronic HCV genotype 4-infected patients: Final results of a phase III trial (Abstract). J Hepatol 2014;60:S535.
96. Feld JJ. Interferon-free strategies with a nucleoside/nucleotide analogue. Semin Liver Dis 2014;34:37-46.
97. Halfon P, Sarrazin C. Future treatment of chronic hepatitis C with direct acting antivirals: is resistance important? Liver Int 2012;32(Suppl 1):79-87.
98. Vermehren J, Sarrazin C. The role of resistance in HCV treatment. Best Pract Res Clin Gastroenterol 2012;26:487-503.
99. Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. Hepatology 2009;50:1709-18.
100. Svarovskaia ES, Dvory-Sobol H, Parkin N, et al. Infrequent development of resistance in genotype 1-6 hepatitis C virus-infected subjects treated with sofosbuvir in phase 2 and 3 clinical trials. Clin Infect Dis 2014;59:1666-74.
101. Kohler JJ, Nettles JH, Amblard F, et al. Approaches to hepatitis C treatment and cure using NS5A inhibitors. Infect Drug Resist 2014;7:41-56.

This is Exhibit "C" referred to in the
Affidavit of DR. VINCE BAIN
sworn (or affirmed) before me at
Edmonton, Alberta,
this 11 day of MARCH, 2015.

Yvan Wachem
A Commissioner for the Province of ALBERTA

Yolanda Van Wachem
Barrister & Solicitor

CIHR CANADIAN HIV TRIALS NETWORK CO-INFECTION AND CONCURRENT DISEASES CORE

Updated Canadian Adult Guidelines for the Treatment of Hepatitis C infection in HIV/Hepatitis Co-infected patients

October 18 2014 – Re-Submitted Version

Mark Hull (MD, FRCPC) University of British Columbia, British Columbia Centre for Excellence in HIV/AIDS

Stephen Shafran (MD, FRCPC) University of Alberta

Alice Tseng (B.Sc.Phm., Pharm.D., FCSHP) Toronto General Hospital

Pierre Giguère (B.Pharm., M.Sc.) The Ottawa Hospital

Marina B. Klein (MD, FRCPC) McGill University

Curtis Cooper (MD, FRCPC) University of Ottawa

On behalf of The CIHR Canadian HIV Trials Network HIV/Hepatitis C Management and Treatment Guidelines Working Group

Corresponding Author:

Curtis Cooper, MD, FRPCP

Associate Professor of Medicine-University of Ottawa

The Ottawa Hospital Division of infectious Diseases

G12-501 Smyth Rd

Ottawa, ON K1H 8L6

+001-613-737-8924 (office)

ccooper@toh.on.ca

Running Head: Canadian Co-Infection Treatment Guidelines (Updated)

Structured Abstract:

Background: HCV co-infection occurs in 20-30% of Canadians living with HIV and is responsible for a heavy burden of morbidity and mortality. HIV-HCV management is more complex due to the accelerated progression of liver disease, the timing and nature of ARV and HCV therapy, mental health and addictions management, socioeconomic obstacles and drug-drug interactions between new HCV direct acting antiviral (DAA) therapies and ARV regimens.

Purpose: Update national standards for management of HCV-HIV co-infected adults in the Canadian context.

Methods: A standing working group with specific clinical expertise in HIV-HCV co-infection was convened by The Canadian Institute of Health Research HIV Trials Network (CTN) to review recently published HCV antiviral data and update Canadian HIV-HCV Co-Infection Guidelines.

Results: Recent data suggest that the gap in SVR rates between HCV mono-infection and HIV-HCV co-infection has been eliminated with newer HCV antiviral regimens. All HIV-HCV co-infected individuals should be assessed for HCV therapy. First line treatment for genotypes 1-6 includes pegylated interferon and weight-based ribavirin dosing plus the nucleotide sofosbuvir for 12 weeks. Sofosbuvir in combination with the protease inhibitor simeprevir for genotype 1 infection is another first line consideration. Sofosbuvir with ribavirin for 12 weeks (genotype 2) and 24 weeks (genotype 3) is also recommended as first line treatment.

Discussion: Recommendations may not supersede individual clinical judgement.

Keywords: HIV, HCV, Co-infection, Treatment, Antivirals, Updated Guidelines

Introduction

Since the publication of the Canadian Co-infection Guidelines in December 2013(1) there have been substantial developments in the field of hepatitis C (HCV) therapeutic management. In addition to the presentation of new information regarding dosing and duration of currently available agents for HCV therapy, two new additional HCV direct-acting antiviral agents (DAAs) have been licensed for use in Canada and the United States. The availability of these agents (sofosbuvir and simeprevir) has required revised recommendations for therapy in HCV mono-infected individuals.(2) Furthermore, it is anticipated that several interferon-free, oral combination DAA regimens will be approved by Health Canada within the year.(3-5) Here we review current protocols for the treatment of HCV in the setting of HIV co-infection and make recommendations for the use of these newer currently available HCV DAAs. These guidelines will continue to be updated on a regular basis as new agents become available for use.

Current HCV therapy in Genotype 1 co-infected patients

The standard of care for genotype 1 HCV-infected individuals since the latter part of 2011 has comprised of triple therapy with pegylated interferon, ribavirin and a HCV protease inhibitor boceprevir or telaprevir. Published phase III studies with both boceprevir and telaprevir in HCV mono-infected populations demonstrate markedly improved SVR rates compared with dual peginterferon plus ribavirin therapy in treatment naïve, prior relapser, prior partial responder and prior null responder populations.(6-9)

Results from two phase II randomized, comparative studies indicate markedly improved sustained virologic response (SVR) outcomes with these triple-therapy regimens for HCV

genotype 1 treatment naïve patients co-infected with HIV.(10, 11) SVR rates achieved in these studies now approximate those seen in mono-infected patients (63-74%), a significant advance over those seen in pegylated interferon/ribavirin trials.(12)

Telaprevir-based therapy in co-infection

A randomized, double-blind, clinical trial compared pegylated interferon α-2a and ribavirin with or without telaprevir in HIV-seropositive, HCV genotype 1-infected patients not on antiretroviral therapy with CD4 counts above 500 cells/μL (n=13, Part A) and in patients receiving suppressive antiretroviral therapy (n=24, Part B).(10) Overall, 74% of patients receiving telaprevir achieved an SVR compared to 45% of those receiving pegylated interferon and ribavirin. Relapse rates were 3% for those receiving telaprevir vs. 15% in those receiving pegylated interferon and ribavirin. SVR rates were similar between those on ART and those who were not. Serious adverse events were seen in 5% of those receiving 48 weeks of fixed duration pegylated interferon α-2a and ribavirin (the majority received fixed 800 mg ribavirin dosing with a few subjects receiving weight-based dosing). Patients were dosed with either 12 weeks of telaprevir 750 mg q8h or an 1125 mg q8h dose was used for patients on efavirenz due to anticipated drug-drug interactions.

Interim analyses from three additional studies now support the use of telaprevir in treatment-experienced co-infected patients. These trials demonstrate comparable outcomes with a twice daily dose of 1125 mg telaprevir in co-infected patients, which has been previously been shown to be non-inferior to standard q8hr dosing in mono-infected individuals.(13) In addition, they provide supportive evidence for the use of response-

guided therapy in HCV treatment-naïve patients and those with prior relapse. Finally these new data provide evidence for the use of telaprevir in treatment-experienced patients, a population not included in the original co-infection trial.

In the UNITE phase 3 open-label study, 182 participants received telaprevir-based therapy (dosed twice daily); treatment-naïve and prior relapsers receiving response-guided therapy if rapid virologic response on treatment was demonstrated, while those without rapid virologic response (RVR – See Table 1 for definitions) as well as prior partial and null responding patients were offered a fixed 48 week course of therapy.(14) The SVR12 rates obtained were similar to those seen previously, with 67% of naïve individuals, 68% of prior relapsers and 60% of partial responders achieving SVR. SVR rates were lower in prior null responder with only 39% achieving SVR12. Overall, 97% experienced an adverse event during therapy, 13% of which were serious adverse events. In the INSIGHT open-label trial, 164 participants (98 of whom were treatment-experienced, including 51 prior null-responders) received standard telaprevir-based therapy dosed three times daily (q8hr) in a similar response-guided algorithm.(15) Complete early virologic response ($cEVR_{12}$) rates were high, with 80% of naïve individuals, 83% of those prior partial response and 57% of null responders achieving undetectable HCV RNA at week 12 of treatment.(15)

In ANRS HC-26 (n=69, 39% relapsers, 31% prior partial responders/breakthrough and 30% non-cirrhotic null responders) participants received a four week lead-in of pegylated interferon and weight-based ribavirin, 12 weeks of triple therapy with the addition of telaprevir, with an additional course of pegylated interferon and ribavirin for a total of 48 or 72 weeks in a response-guided fashion dependent on results of the week 8 (week 4

triple therapy outcome).(16) Patients were included if they had stable CD4 cell counts > 200 cells/μL (CD4% >15%) with suppressed HIV viral load on efavirenz, atazanavir/ritonavir or raltegravir-based regimens. The METAVIR score was F3 in 16% and 23% were cirrhotic (F4). Sustained virologic response (SVR24 response – see Table 1) was achieved in 80% of individuals and did not appear to be influenced by the fibrosis stage (F1-2 83%, F3-4 78%), or previous response type (with EOT achieved by those with prior relapse 74%, prior breakthrough 83%, partial response 100% and prior null response 71%), although sample size for these sub-groups was small. Grade 4 adverse events occurred in 22% of cases, including anemia (10%) and infections (3%). Dose reduction of pegylated interferon or ribavirin was required in 22% and 43%, respectively.Sixty-five percent of study participants were administered erythopoietin and 23% required blood transfusion during the extended course of therapy.(17)

Boceprevir-based therapy in co-infection

Boceprevir was evaluated in 98 co-infected patients in a placebo-controlled randomized trial.(11) All patients were on antiretroviral therapy with stable, HIV suppression. Antiretroviral regimens allowed in this study consisted of a ritonavir-boosted protease inhibitor, raltegravir, or maraviroc in conjunction with two nucleoside inhibitors other than zidovudine, stavudine or didanosine. Most participants were receiving atazanavir, lopinavir, or darunavir-based regimens. Non-nucleoside reverse transcriptase inhibitor based regimens were not allowed in this protocol. Only 5 of 98 participants were cirrhotic. All participants received 48 weeks of therapy consisting of standard four week lead-in phase with pegylated interferon α-2b and weight-based ribavirin, followed by a fixed duration of 44 weeks of boceprevir 800 mg q8h or placebo. Overall, an SVR24 was

achieved in 63% of triple therapy recipients (n=64) versus 29% of pegylated interferon α-2b and ribavirin treated study participants (n=34).(11) Adverse events were common in those receiving boceprevir (41% vs. 26%). Despite the successful use of HIV protease inhibitors in this trial, subsequent pharmacokinetic studies have suggested potential for significant interactions (See Table 2 – Drug Interactions with HCV DAAs).

In ANRS HC-27, treatment–experienced patients (n=64), received a standard lead-in phase followed by 44 weeks of triple therapy with boceprevir.(18) Individuals with cirrhosis and prior null response to pegylated interferon and ribavirin were excluded. Those without a week 8 RVR completed an additional 24 weeks (total 72 weeks) of pegylated interferon with ribavirin. The overall SVR12 rate was 53%, with SVR rates of 90% in prior relapsers, 61% in those with partial response and 24% in null responders. In this trial there was an apparent difference in outcome based on underlying ART regimen, with a 41% SVR rate in those receiving atazanavir/ritonavir compared to 70% in those receiving raltegravir.(19)

Conclusion

These results demonstrate that response rates for treatment naïve patients is improved with pegylated interferon, ribavirin and an HCV protease inhibitor compared to SVR rates achieved with pegylated interferon/ribavirin alone. SVR rates approximate those seen in mono-infection with reduced SVR rates observed in those with more advanced disease. In addition, the encouraging interim findings suggest that treatment-experienced co-infected patients will achieve SVR outcomes similar to those seen in mono-infected trials, with highest SVR rates in prior relapsers (higher than treatment naïve patients),

intermediate SVR rates in prior partial responders and the lowest SVR rates in prior null responders. Adverse events, particularly anemia, were common but similar in characteristic and rate to that of HCV mono-infected treatment recipients. These results highlight the need for improved therapeutic options for all HCV-infected individuals with advanced disease or prior treatment failure.

Next Generation DAAs: simeprevir and sofosbuvir

Two new DAAs have recently been approved in Canada and the United States for the treatment of HCV; the NS3/4A protease inhibitor simeprevir, and the novel uridine nucleotide NS5B RNA-dependent RNA polymerase inhibitor sofosbuvir. These agents offer marked improvement over current therapies, as they have much improved side effect profiles, fewer drug interactions, reduced pill burden and in the case of sofosbuvir, offer pan-genotypic coverage with the potential for interferon-free based therapy for all genotypes. As such, they have superseded the use of both telaprevir and boceprevir in current treatment recommendations in the United States.(20)

Simeprevir

Simeprevir is a second-wave NS3/4A protease inhibitor, which offers a number of advantages over boceprevir and telaprevir. The recommended dose in adults with genotype 1 infection is 150 mg once daily with food. Food delays the absorption of simeprevir, increasing the time to reach maximum plasma concentration by 1 to 1.5 hours, and increases the exposure of simeprevir by approximately 60%. Simeprevir is available as a 150 mg capsule, allowing for a significant reduction in pill burden compared to its predecessors in this class. Simeprevir is a substrate of CYP3A4, and a

mild inhibitor of intestinal (but not hepatic) CYP3A4, 1A2, P-glycoprotein (P-gp) and Organic anion transporting polypeptides (OATP) 1B1 (20). Simeprevir has no clinically relevant effects on CYP2C9, 2C19 and 2D6.(20) Due to these characteristics, simeprevir is primarily the subject, rather than a perpetrator of pharmacokinetic drug-drug interactions. Co-administration of simeprevir with moderate-strong inducers or inhibitors of CYP3A4 is not recommended due to the potential for significant alterations in simeprevir plasma concentrations. Clinically, this restricts antiretroviral choices for HIV/HCV co-infected patients, as regimens including ritonavir or cobicistat as a booster or the NNRTIs efavirenz, etravirine and nevirapine should not be used [Table 2,3]. Similarly, other inducing/inhibiting agents such as anticonvulsants, rifamycins, dexamethasone, azole antifungals and macrolides should be avoided with simeprevir. In the transplant population, simeprevir may be preferred over telaprevir or boceprevir due to the absence of drug interactions with tacrolimus and cyclosporine.(21)

Use of simeprevir in conjunction with pegylated interferon and ribavirin has been shown to achieve similar improvement in SVR rates in phase II studies, in both naïve and experienced HCV mono-infected patients.(22, 23) Simeprevir used in a response-guided protocol has been assessed in three large phase III clinical trials in HCV monoinfected treatment naïve individuals (QUEST-1, QUEST-2) and prior relapsers (PROMISE).(24-26) In these trials, simeprevir 150 mg daily for the initial 12 weeks of triple therapy with response-guided pegylated interferon/ribavirin for 24 or 48 weeks resulted in SVR12 rates of 80-81% in naïve individuals compared to 50% for those receiving pegylated interferon/ribavirin alone. Overall, amongst naïve individuals, the majority (80% in QUEST-1 and 91% in QUEST-2) met criteria for response-guided therapy (i.e. 24 weeks

total), based on a HCV PCR <25 IU/mL at week 4 with undetectable HCV RNA at week 12. Response rates amongst those who met these criteria were high at 86-91%. Prior relapsers showed similar benefit with 79% of those treated with simeprevir achieving SVR12 compared to 37% in the control arm.(26) The majority of individuals (92.7%) were eligible for response-guided therapy and of those 83% achieved SVR12.

Data in treatment-experienced HCV mono-infected patients is derived from the Phase 2 ASPIRE trial(23) wherein those individuals who received 48 weeks of pegylated interferon and ribavirin had SVR24 rates of 88% in prior relapsers, 86% in prior non-responders and 58% in prior null responders. Recently, the results of the phase 3 ATTAIN trial, the only head-to-head randomized trial of two HCV protease inhibitors, showed comparable SVR rates with 12 weeks of simeprevir vs. 12 weeks of telaprevir, each given with 48 weeks of pegylated interferon alfa-2a for 48 weeks in patients with HCV genotype 1 infection who were partial or null responders to prior dual therapy with peginterferon plus ribavirin.(27) Specifically, SVR12 rates were 70% and 44% in partial and null responders, respectively, treated with simeprevir versus 69% and 46%, respectively, in those treated with telaprevir. There was a lower incidence of anemia and fewer discontinuations for adverse events in simeprevir recipients.

The side effect profile for individuals receiving simeprevir was similar to those on pegylated interferon and ribavirin, with no significant additional toxicities identified. A naturally occurring HCV NS3 polymorphism – the Q80K mutation was associated with reduced SVR rates in genotype 1a patients. This polymorphism occurs in about 45% of North Americans with genotype 1a(28) but only ~18% of Europeans.(29) In the QUEST-1 study those with this mutation had no better response rate with the addition of

simeprevir compared to those in the pegylated interferon/ribavirin arm.(24) Screening at baseline for this mutation in genotype 1a is recommended.

Data in co-infected patients

Simeprevir has been evaluated in treatment naïve and experienced HIV co-infected patients.(30) In the C212 open-label phase III study, 106 individuals received either response-guided therapy for naïve/relapsers (n=64) or standard 12 weeks of triple therapy followed by 36 weeks of pegylated interferon/ribavirin in treatment-experienced patients or those with underlying cirrhosis. Due to potential drug interactions, ART regimens were limited to raltegravir, maraviroc or rilpivirine, with either tenofovir/emtricitabine or abacavir/lamivudine. Overall SVR12 rates were achieved in 79% of naïve individuals, 87% of prior relapsers, 70% of prior partial responders and 57% of null responders. Response rates were reduced in those with cirrhosis (64%) vs. non-cirrhotics (80%) and side effect profile was similar to what is expected with peginterferon plus ribavirin alone.

Sofosbuvir

Sofosbuvir is a nucleotide pro-drug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate, GS-461203 which is incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. Sofosbuvir is available as a 400 mg tablet. The approved dose in adults is 400 mg once daily taken without regard to food. After oral administration, sofosbuvir is rapidly converted to the predominant circulating metabolite GS-331007. Sofosbuvir and GS-331007 do not inhibit any CYP450 isoenzymes or UGT1A1. Sofosbuvir is a P-gp substrate and breast cancer resistance protein (BCRP) substrate whereas GS-331007 is not. Sofosbuvir should not be

coadministered with potent P-gp inducers such as rifampin or St. John's wort.(31) Significant interactions have not been demonstrated or are not expected between sofosbuvir and antiretrovirals.

Sofosbuvir has been widely evaluated in HCV mono-infected individuals. In the phase III NEUTRINO study, 291 genotype 1-infected treatment naïve individuals received 12 weeks of triple therapy with sofosbuvir 400 mg daily in conjunction with pegylated interferon and ribavirin.(32) Overall SVR12 rates were achieved in 89% of individuals, with lower rates seen in those with cirrhosis than in those without (80% vs. 92%). Side effects appear to be driven predominantly by the receipt of pegylated interferon/ribavirin, but a control group for definitive comparison was not built into the study design. In addition, use of sofosbuvir with ribavirin alone has been evaluated for interferon-ineligible patients with genotype 1 infection. In a small (n=60) phase II study, sofosbuvir with weight-based ribavirin for 24 weeks achieved an SVR24 rate of 68% in individuals deemed to be interferon-ineligible.(33) A relatively high rate of relapse (54%) was seen in those with more advanced disease. Other small trials (ELECTRON, QUANTUM trials) of this interferon-sparing strategy have found SVR rates ranging from 50%-84%.(34, 35)

Limited data exist for treatment-experienced patients. However, given the response seen in individuals with characteristics that would normally be considered unfavourable for response to pegylated interferon and ribavirin, modelling conducted during the approval of sofosbuvir by the United States Food and Drug Administration (FDA) predicts an approximate 78% response in treatment-experienced patients.(36)

Genotypes 2 and 3 HCV Mono-Infection

Sofosbuvir has also been evaluated for use in genotypes 2 and 3 in an initial large non-inferiority comparison to standard pegylated interferon/ribavirin.(32) In the FISSION trial, 499 treatment naïve individuals were randomized to 12 weeks of therapy with sofosbuvir/ribavirin or 24 weeks of pegylated interferon/ribavirin. Individuals with genotype 2 infection had exceptional SVR rates of 97% with sofosbuvir/ ribavirin vs. 76% with pegylated interferon/ribavirin, while those with genotype 3 achieved similar SVR rates to pegylated interferon/ribavirin (56% vs. 63%). Cirrhosis markedly reduced SVR rates for genotype 3 individuals to approximately 30% in both arms. Similar SVR rates were seen in the POSITRON trial in interferon-ineligible patients.(37) In the phase III VALENCE study, improved SVR rates were seen in genotype 3 treatment naïve individuals who received 24 weeks of sofosbuvir/ribavirin with SVR rates 94%, with the sub-group of cirrhotic patients achieving SVR of 90%.(38)

Sofosbuvir has also been evaluated in treatment-experienced genotype 2 and 3 patients. In the FUSION trial, individuals were randomized to receive 12 or 16 weeks of therapy with sofosbuvir and ribavirin. Those with genotype 2 achieved an SVR rate of 86% after 12 weeks and 94% after 16 weeks. SVR rates were much lower for genotype 3, with an SVR rate of 30% in those receiving 12 weeks vs. 62% in those who received 16 weeks of therapy. (37) In the VALENCE study, treatment-experienced genotype 2 patients experienced similar high rates of response (91%) after 12 weeks of therapy of dual therapy. Treatment-experienced patients with genotype 3 treated with 24 weeks of sofosbuvir and ribavirin achieved an SVR of 87% in those without cirrhosis, and only 60% in those with cirrhosis.(39) In the LONESTAR-2 phase II trial, the addition of

pegylated interferon to a 12 week course of sofosbuvir/ribavirin resulted in SVR rates of 83% for genotype 3, with or without cirrhosis.(40)

Data in HIV-HCV co-infected patients

Sofosbuvir was evaluated in HIV co-infected patients in the phase II Study 1910 trial.(41) In this open-label study, 23 co-infected treatment-naïve individuals received sofosbuvir 400 mg daily in conjunction with pegylated interferon and weight-based ribavirin for 12 weeks. Individuals were predominantly genotype-1 infected, with two individuals with genotype 3, and a single individual with genotype 2 and 4 respectively were also enrolled. The ART regimens included efavirenz, rilpivirine, raltegravir and the boosted protease inhibitors atazanavir and darunavir. Overall, the SVR12 was 91%. Side effects were predominantly those of pegylated interferon and ribavirin.

In the Phase III PHOTON-1 study, three cohorts of co-infected patients (genotype 1 treatment naïve patients n=114, genotype 2 (n=28) and 3 (n= 42) naïve patients, and genotypes 2/3 treatment-experienced patients (n=41) were enrolled to receive either 12 weeks or 24 weeks (genotype 1 and treatment-experienced patients) of sofosbuvir with ribavirin.(42) Individuals could be on a wide range of ART regimens due to the lack of drug interactions, or naïve to ART if baseline CD4 cell count was > 500 cells/mm^3. The majority of those enrolled were on ART, receiving predominantly efavirenz, atazanavir or darunavir-based regimens. The SVR24 rate was 75% for genotype 1 participants, 88% for genotype 2, and 67% for genotype 3 patients. Amongst treatment-experienced patients, SVR24 was attained by 92% of genotype 2 and 88% of genotype 3 individuals.

Overall, the regimen was well tolerated, with more adverse events related to sofosbuvir/ribavirin seen in those receiving a 24-week course of therapy.

DAA combination regimens of currently approved agents

Proof of concept studies of interferon-free and ribavirin-sparing combinations of potent DAA agents have rapidly advanced the potential for simple, potent and well-tolerated therapies for HCV.(43-45) Further evaluation of combination DAA therapy has demonstrated potential therapy in patients with advanced disease, in prior null responders and as salvage therapy in patients previously non-responsive to telaprevir and boceprevir-based therapy.(3, 46, 47) In the COSMOS study, HCV mono-infected, treatment naïve and prior null responders with HCV genotype 1 mono-infection, received once daily simeprevir and sofosbuvir, with or without ribavirin for either 12 or 24 weeks.(46) In the first cohort of 80 null responders with METAVIR F0-F2 disease, SVR12 rates with dual therapy were high at 92-93% after 12 or 24 weeks of therapy, and the addition of ribavirin was not clearly associated with improvement in SVR rates.(48) For the second cohort of 87 naïve and null responders with F3-F4 disease, SVR12 rates were 93% with 12 weeks of therapy and 96% with 24 weeks of therapy.(49) The addition of ribavirin did not increase SVR rates but did result in some cases of anemia.(4) On the basis of the COSMOS data, two phase 3 studies, will evaluate 8 vs. 12 weeks of sofosbuvir plus simeprevir in non cirrhotics (OPTIMIST-1) and 12 weeks in cirrhotics (OPTIMIST-2) in HCV genotype 1 mono-infected treatment naïve patients.(50) Ribavirin will not be included in the phase 3 studies. At present, no data exist for this combination in co-infected individuals.

Future DAA combinations

Interferon-free, combination DAA regimens have been or soon will be approved by regulatory agencies, including Health Canada. We anticipate that the regimens mentioned below will rapidly be identified as first line therapies for HCV. However, as HIV-HCV co-infection specific clinic trials evaluating these new regimens have yet to be published, they have not been included in this current iteration of the CIHR CTN HIV-HCV co-infection guidelines.

The combination of sofosbuvir with a NS5A replication inhibitor is particularly promising. This was first demonstrated in a phase 2 study with the NS5A inhibitor daclatasvir, with SVR rates of 98% in genotype 1, 92% in genotype 2 and 89% in genotype 3.(51) Moreover, the combination of sofosbuvir plus daclatasvir resulted in SVRs in 100% of 41 patients who previously failed triple therapy with peginterferon, ribavirin and either telaprevir or boceprevir.

Very recently, three phase 3 trials of the fixed-dose combination of sofosbuvir with the NS5A inhibitor ledipasvir, with and without ribavirin for 8 or 12 weeks in patients with HCV genotype 1 mono-infection demonstrated SVR rates of 93 to 99%, including boceprevir or telaprevir treatment experienced patients and those with cirrhosis.(4, 52) The addition of ribavirin did not increase SVR rates. A New Drug Application (NDA) for sofosbuvir-ledipasvir was filed with the US FDA on February 10, 2014 and received approval in the United States and Canada in October 2014.(53) The combination of sofosbuvir/ledipasvir for 12 weeks is currently under study in HIV/HCV co-infected patients in the ION-4 protocol.

The combination of 3 DAAs, specifically the NS3 protease inhibitor ABT-450 boosted by the CYP3A4 inhibitor ritonavir, the NS5A inhibitor ombitasvir and the NS5B non nucleoside polymerase inhibitor dasabuvir, with ribavirin given for 12 weeks results in SVR rates of 93 to 99% in HCV genotype-1 mono-infected patients, including treatment experienced patients and those with cirrhosis.(5, 54, 55) It appears that ribavirin can be omitted in genotype 1b, but is needed in genotype 1a.(56) A new drug application (NDA) for this regimen was filed with the FDA on April 22, 2014.(57) This regimen is currently under evaluation in the HCV/HIV co-infected patients (TURQUOISE I study). However, the presence of multiple CYP3A4 metabolized medications, including ritonavir, may limit antiretroviral treatment options in HIV co-infected patients considered for this regimen.

Summary

Taken together, these clinical trial results indicate a significant paradigm shift in the management of HCV mono and co-infection is imminent, pending regulatory approvals and eventual addition to provincial formularies. Recent data suggest that the gap in SVR rates between HCV mono-infection and HIV-HCV co-infection has been eliminated with newer HCV antiviral regimens. The "real-world" uptake and efficacy of these agents in vulnerable populations will be important to assess their impact on the burden of HCV disease and sequelae.(1)

Recommendations for Therapy

1. **Genotype 1 Treatment-Naïve Individuals without Cirrhosis**

First Line: Sofosbuvir 400 mg daily with pegylated interferon and weight-based ribavirin for 12 weeks of therapy. This combination offers short duration of therapy with high SVR rate with no concerns regarding ART drug interactions, and no additional side effects beyond that of pegylated interferon and ribavirin. (Class 1, Level B) (see Appendix for level of evidence criteria)

Alternative: Sofosbuvir 400 mg daily with simeprevir 150 mg daily. This regimen has not been evaluated in co-infection. However, based on the SVR rates achieved in other traditionally 'hard-to-cure' populations (i.e. treatment-experienced individuals with cirrhosis), this combination can be considered preferable where available. (Class 1, Level C)

Alternative: Therapy for interferon-eligible patients would consist of response-guided therapy with simeprevir 150 mg daily with pegylated interferon and weight-based ribavirin. (Class 1, Level B)

a) Genotype 1a strains must undergo Q80K polymorphism testing prior to use of this regimen, and an alternative DAA should be chosen if Q80K is present.

b) Response-guided therapy with treatment discontinuation at week 24 can be offered if week 4 RNA < 25 IU/mL is attained, but should not be used in individuals with underlying cirrhosis in whom a full 48 week course of pegylated interferon and ribavirin is advised.

c) Drug interactions with ART must be considered with use of simeprevir.

Alternative: Interferon-ineligible individuals can be considered for 24 weeks of sofosbuvir 400 mg daily and weight-based ribavirin. Given the decreased SVR rates seen with this combination, and limited information in those with cirrhosis, deferral of therapy for future combination DAA regimens should be considered. (Class 1, Level B)

2. Genotype 1 Treatment Naïve Individuals with Cirrhosis

First Line: Sofosbuvir 400 mg daily pegylated interferon and ribavirin for 12 weeks. Patients must not have decompensated cirrhosis to receive interferon. (Class 1 , Level B)

Alternative: Sofosbuvir 400 mg daily with simeprevir 150 mg daily for 12 weeks. This regimen has not been evaluated in co-infection. However, based on the SVR rates achieved in other traditionally 'hard-to-cure' populations (i.e. treatment-experienced individuals with cirrhosis), this combination can be considered preferable where available. (Class 1, Level C)

Alternative: Simeprevir 150 mg daily for 12 weeks with pegylated interferon and ribavirin for 48 weeks (assuming genotype 1a recipient is Q80K negative). (Class 1, Level B)

3. Genotype 1 Treatment-Experienced Patients with Prior Relapse (with or without cirrhosis)

See recommendations for Genotype 1 treatment-naïve individuals with or without cirrhosis as above. Retreatment with pegylated interferon, ribavirin and simeprevir is not

recommended in prior relapsers, partial or null responders to other protease inhibitor (boceprevir,telaprevir)-based regimens. (Class 1, Level B)

4. **Genotype 1 Treatment-Experienced Patients - Prior Non-Responders or Null Responders (with or without cirrhosis)**

First Line: Sofosbuvir 400 mg daily with simeprevir 150 mg daily for 12 weeks (NB-based on HCV mono-infection studies). (Class 1, Level C)

Or

First Line: Sofosbuvir 400 mg daily with pegylated interferon and weight-based ribavirin for 12-24 weeks. (Class 1, Level C)

Alternative: Simeprevir 150 mg daily for 12 weeks with 48 weeks of pegylated interferon and weight-based ribavirin (except in genotype 1a with Q80K). Response-guided therapy is recommended for non-cirrhotic patients with prior relapse, whereas 48 weeks is recommended in prior partial or null responders, with or without cirrhosis. (Class 1, Level B)

5. **Genotype 2 Treatment Naïve Patient**

First Line: Sofosbuvir 400 mg daily with weight-based ribavirin for 12 weeks. (Class 1, Level B)

6. **Genotype 2 Treatment-Experienced Patient**

First Line: Sofosbuvir 400 mg daily with ribavirin for 24 weeks. (Class 1, Level B)

Alternative: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (Class 1, Level C)

Recommendations for treatment-experienced co-infections are based on expert recommendation, utilizing data from a single trial in co-infection and data from other hard-to-cure mono-infected populations.

7. Genotype 3 Treatment-Naïve Patient

First Line: Sofosbuvir 400mg daily with pegylated interferon and ribavirin for 12 weeks, particularly if compensated cirrhosis is present and interferon is not contra-indicated. (Class 1, Level C)

OR

First Line: Sofosbuvir 400 mg daily with ribavirin for 24 weeks if interferon contra-indicated or patient considered interferon-ineligible. (Class 1, Level B)

8. Genotype 3 Treatment-Experienced Patient

First Line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (Class 1, Level C)

Alternative: Sofosbuvir 400mg daily with ribavirin for 24 weeks if interferon ineligible or intolerant (Class 1, Level B)

9. Genotype 4 Treatment-Naive and Experienced

First Line: Sofosbuvir 400 mg daily with pegylated interferon and ribavirin for 12 weeks. (NB- based on HCV mono-infection studies) (Class 1, Level C)

There is currently insufficient data in HIV-HCV co-infection with genotype 4-6 to comment on the efficacy of sofosbuvir-simeprevir. Likewise, there is currently

insufficient data in HIV-HCV co-infection with genotype 5-6 to comment on the efficacy of sofosbuvir with pegylated interferon and ribavirin.

Regimens no longer recommended for first line use:

1. Telaprevir and boceprevir are no longer recommended for first line use given the improved safety and tolerability profiles of the new DAA agents.
2. Pegylated interferon and ribavirin as dual therapy for genotype 2/3 individuals.

Circumstances may exist in which first line regimens are not accessible to patients (e.g. restricted funding). The above second line regimens could be considered as treatment options. However, the patient must be fully aware of the diminished likelihood for cure and/or increased likelihood for adverse events compared to first line regimens.

Timing of initiation of HCV therapy in the era of DAAs

At this time it is unclear whether access to newer agents will be standard across the country, and/or which, if any, additional criteria may be imposed by individual provinces/payers to limit access to DAAs given the anticipated costs of these agents. Recommendations for use of newer DAA agents/combinations is based primarily on a review of the currently available data evaluating efficacy and safety in mono-infected and co-infected patients.

Access to appropriate therapy when clinically indicated has long been recommended in Canada by experts involved in the care of patients living with HCV(58) and we would continue to advocate for such an approach for co-infected patients. The authors recognize that due to potential restrictions to access and reimbursement of newer drugs/regimens

for HCV, clinicians and patients may face difficult decisions regarding therapy. In this situation alternate options may be considered.

a. Deferral of therapy

Individuals with early fibrosis may be able to defer therapy compared to those with more advanced disease, as they have lower risk of medium-term progression of disease. These individuals may be able to wait for future combinations and potentially improved access to interferon-free based combinations. If deferral of therapy is considered, updated staging for fibrosis progression is recommended on an annual basis if access to transient elastography is possible, or every 3 years if liver biopsy is to be performed. The clinician must also consider that for dual therapy with pegylated interferon plus ribavirin and triple therapy with pegylated interferon plus one DAA, SVR rates are highest at early fibrosis stages (<F3) and decrease with advancing disease.

Additional considerations of patient readiness, and consideration of possible onward HCV transmission risk for individuals in a core transmitter group (IDU and certain MSM populations) compared to those without high risk for transmission [e.g. many baby boomers (born between approximately 1945-1970)] may influence a decision to consider delaying therapy.

b. Utilization of non-preferred regimens

For cost/access reasons, it may be necessary to use older therapies for HCV with a higher incidence of adverse effects and lower SVR rates in some patients. In all such cases,

patients should be made aware of the existence of newer improved therapies and given the option of potentially paying for them, if they so choose.

References

1. Hull M, Klein M, Shafran S, Tseng A, Giguere P, Cote P, et al. CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Canadian guidelines for management and treatment of HIV/hepatitis C coinfection in adults. Can J Infect Dis Med Microbiol. 2013 Winter;24(4):217-38.

2. Recommendations for testing, managing, and treating hepatitis C. [Web Page]: American Association for the Study of Liver Diseases and the Infectious Diseases Society of America; 2014 [cited 2014 April 24]; Available from: http://www.hcvguidelines.org.

3. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014 Feb 8;383(9916):515-23.

4. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.

5. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1594-603.

6. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

7. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.

8. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011 Jun 23;364(25):2405-16.

9. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.

10. Sulkowski MS, Sherman KE, Dieterich DT, Bsharat M, Mahnke L, Rockstroh JK, et al. Combination Therapy With Telaprevir for Chronic Hepatitis C Virus Genotype 1 Infection in Patients With HIV: A Randomized Trial. Ann Intern Med. 2013 Jul 16;159(2):86-96.

11. Sulkowski M, Pol S, Mallolas J, Fainboim H, Cooper C, Slim J, et al. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. Lancet Infect Dis. 2013 Jul;13(7):597-605.

12. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med. 2004 Jul 29;351(5):438-50.

13. Buti M, Agarwal K, Horsmans Y, Sievert W, Janczewska E, Zeuzem S, et al. Telaprevir twice daily is noninferior to telaprevir every 8 hours for patients with chronic hepatitis C. Gastroenterology. 2014 Mar;146(3):744-53 e3.

14. Hare CD, Sherman K, Talal AH, et al. Simplified Dosing and Response-Guided Therapy Using Telaprevir Combination Treatment for Genotype 1 HCV Treatment-Naïve or -Experienced HIV Co-infected Patients: UNITE Interim Analysis. (Abstract 64). Proceedings and Abstracts of HEP DART 2013; December 8-12; Big Island, HI, USA2013.

15. Montes M, Nelson M, M. G, et al, editors. Telaprevir combination therapy in treatment-naive and experienced patients co-infected with HCV and HIV. (Abstract 38). Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

16. Cotte L, Braun J, Lascoux-Combe C, Vincent C, Pol S, Valentin M, et al., editors. High Early Virologic Response with Telaprevir-Pegylated Interferon-Ribavirin in Treatment-experienced HCV Genotype 1/HIV Co-infected Patients: ANRS HC26 TelapreVIH Study. (Abstract 36). 20th Conference on Retroviruses and Opportunistic Infections; 2013 March 3-6; Atlanta, GA.

17. Cotte L, Braun J, Lascoux-Combe C, Vincent C, Valantin M, Sogni P, et al. Telaprevir for HIV/Hepatitis C Virus-Coinfected Patients Failing Treatment With Pegylated Interferon/Ribavirin (ANRS HC26 TelapreVIH): An Open-Label, Single-Arm, Phase 2 Trial. Clin Infect Dis. 2013 Aug 18, 2014.

18. Poizette-Martin I, Bellissant E, Piroth L, et al, editors. W48 Response Rate of Boceprevir-PegIFN-RBV in Treatment-Experienced HIV Coinfected Patients with HCV genotype 1: ANRS-HC27 BocepreVIH Study. (Abstract 1105). Program and Abstracts of the 64th American Association for the Study of Liver Diseases; 2013 November 7-11; Washington, DC.

19. Poizette-Martin I, Bellissant E, Colson P, Renault A, Piroth L, Solas C, et al., editors. Boceprevir for Previously Treated HCV-HIV Coinfected Patients: The ANRS-HC27 BocepreVIH Trial. (Abstract 659LB). Abstracts and Proceedings of the 21st Conference on Retroviruses and Opportunistic Infections (CROI); 2014 March 3 - 6; Boston, MA.

20. Galexos (simeprevir) Product Monograph. Janssen Inc. Toronto, ON2013.

21. Ouwerkerk-Mahadevan S, Simion S, Mortier E, et al, editors. No clinically significant interaction between the investigational HCV protease inhibitor simeprevir (TMC435) and the immunosuppressive agents cyclosporine and tacrolimus. (Abstract 80) Abstracts and Proceedings of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2012 November 9-13; Boston, MA.

22. Fried MW, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, et al. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. Hepatology. 2013 Dec;58(6):1918-29.

23. Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. Gastroenterology. 2014 Feb;146(2):430-41 e6.

24. Jacobson IM, Dore GJ, Foster GR, al. E, editors. Simeprevir (TMC435) with peginterferon/ribavirin for chronic HCV genotype-1 infection in treatment-naive patients: results from QUEST-1, a phase III trial. (Abstract 1425). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, The Netherlands.

25. Manns M, Marcellin P, Poordad F, et al. Simeprevir (TMC435) with peginterferon/ribavirin for treatment of chronic HCV genotype-1 infection in treatment-naive patients: results from QUEST-2, a phase III trial. (Abstract 1413). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; April 24-28; Amsterdam, The Netherlands2013.

26. Forns X, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, et al. Simeprevir With Peginterferon and Ribavirin Leads to High Rates of SVR in Patients With HCV Genotype 1 Who Relapsed After Previous Therapy: A Phase 3 Trial. Gastroenterology. 2014 Jun;146(7):1669-79 e3.

27. Reddy KR, Zeuzem S, Zoulim F, et al, editors. A Phase III randomised, double-blind study to evaluate the efficacy, safety and tolerability of simeprevir vs telaprevir in combination with pegylated interferon and ribavirin in chronic hepatitis C virus genotype 1 treatment-experienced patients: the ATTAIN study. Proceedings and Abstracts of the Asian Pacific Association of the Study of the Liver; 2014 March 12-14; Brisbane, Australia.

28. Andonov A, Kadkhoda K, Osiowy C, Kaita K. Pretreatment resistance to hepatitis C virus protease inhibitors boceprevir/telaprevir in hepatitis C virus subgenotype 1a-infected patients from Manitoba. Can J Gastroenterol. 2013 Jul;27(7):414-6.

29. Vicenti I, Rosi A, Saladini F, Meini G, Pippi F, Rossetti B, et al. Naturally occurring hepatitis C virus (HCV) NS3/4A protease inhibitor resistance-related mutations in HCV genotype 1-infected subjects in Italy. J Antimicrob Chemother. 2012 Apr;67(4):984-7.

30. Dieterich D, rockstroh J, Orkin C, Gutierrez F, Klein M, Reynes J, et al. Simeprevir (TMC435) with Peginterferon/Ribavirin in Patients Coinfected with HCV Genotype-1 and HIV-1: A Phase III Study. Clin Infec Dis [serial on the Internet]. 2014; (pii).

31. SOVALDI Product Monograph. Gilead Sciences Canada, Inc. Mississauga, ON2013.

32. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.

33. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. Jama. 2013 Aug 28;310(8):804-11.

34. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):34-44.

35. Lalezari J, Nelson D, Hyland RH, et al, editors. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. (Abstract 845). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, The Netherlands.

36. Muir A, Nelson D, Gordon S, et al, editors. Modeling predicts clinically meaningful SVR rates in genotype 1 treatment-experienced patients based on results in genotype 1 treatment-naive patients treated with sofosbuvir+ peginterferon+ ribavirin for 12 weeks. (Abstract P1220). Abstracts and Proceedings of the 49th European Association for the Study of the Liver meeting; 2014 April 9-13; London, UK.

37. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 May 16;368(20):1867-77.

38. Zeuzem S, Dushelko GM, Salupere R, et al, editors. Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE trial. (Abstract 1085) Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

39. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014 May 22;370(21):1993-2001.

40. Lawitz E, Poordad F, Brainard D, et al, editors. Sofosbuvir in combination with pegIFN and ribavirin for 12 weeks provides high SVR rates in HCV-infected genotype 2 or 3 treatment experienced patients with and without compensated cirrhosis: results from the LONESTAR-2 study. (Abstract LB4) Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

41. Rodriguez-Torres M, Rodriguez-Orengo J, Gaggar A, et al, editors. Sofosbuvir and Peginterferon Alfa-2a/Ribavirin for Treatment-Naïve Genotype 1–4 HCV-Infected Patients Who Are Coinfected With HIV. (Abstract 714). Abstracts and Proceedings of IDWeek; 2013 October 2-6; San Francisco, CA.

42. Sulkowski M, Naggie S, Lalezari J, Fessel W, Mounzer K, Shuhart M, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA. 2014 July 23-30, 2014;312(4):353-61.

43. Lok AS, Gardiner DF, Lawitz E, Martorell C, Everson GT, Ghalib R, et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012 Jan 19;366(3):216-24.

44. Poordad F, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med. 2013 Jan 3;368(1):45-53.

45. Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Mullhaupt B, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med. 2013 Aug 15;369(7):630-9.

46. Jacobson IM, Ghalib R, Rodriguez-Torres M, et al, editors. SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS7977) with or without ribavirin in cirrhotic and non-cirrhotic HCV genotype 1 treatment-naive and prior null responder patients: the COSMOS study. (Abstract LB3). Program and abstracts of the 64th Annual Meeting of the American Association for the Study of Liver Diseases; 2013 November 1-5; Washington, DC.

47. Sulkowski M, Gardiner DF, Rodriguez-Torres M, et al, editors. Sustained virologic response with daclatasvir plus sofosbuvir ± ribavirin (RBV) in chronic HCV genotype (GT) 1-infected patients who previously failed telaprevir (TVR) or

boceprevir (BOC). (Abstract 1417). Program and abstracts of the 48th Annual Meeting of the European Association for the Study of the Liver; 2013 April 24-28; Amsterdam, The Netherlands.

48. Sulkowski M, Jacobson IM, Ghalib R, et al, editors. Once-daily simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin in HCV genotype 1 prior null responders with Metavir F0-2: COSMOS study subgroup analysis. (Abstract 07). Abstracts and Proceedings of the 49th Annual Meeting of the European Association for the Study of the Liver; 2014 April 9-13; London, UK.

49. Lawitz E, Ghalib R, Rodriguez-Torres M, et al, editors. Simeprevir plus sofosbuvir with/without ribavirin in HCVgenotype 1 prior null-responder/treatment-naive patients (COSMOS study): primary endpoint (SVR12) results in patients with Metavir F3-4 (Cohort 2). (Abstract O165). Abstracts and Proceedings of the 49th Annual Meeting of the European Association for the Study of the Liver; 2014 April 9-13; London, UK.

50. Janssen Initiates Phase 3 OPTIMIST Trials of Once-Daily Simeprevir in Combination with Once-Daily Sofosbuvir for the Treatment of Genotype 1 Chronic Hepatitis C [PDF]: Janssen Pharmaceutical Companies; [updated April 2, 2014; cited 2014 May 30]; Available from: http://www.janssenrnd.com/sites/default/files/pdf/OPTIMIST-Press_Release_FINAL_4%201_14_v3_clean.pdf#zoom=125.

51. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014 Jan 16;370(3):211-21.

52. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis. N Engl J Med. 2014(370):1879-88.

53. Gilead Files for U.S. Approval of Ledipasvir/Sofosbuvir Fixed-Dose Combination Tablet for Genotype 1 Hepatitis C. [Web Page]: Gilead Sciences, Inc.; [updated February 10, 2014; cited 2014 May 30]; Available from: http://www.gilead.com/news/press-releases/2014/2/gilead-files-for-us-approval-of-ledipasvirsofosbuvir-fixeddose-combination-tablet-for-genotype-1-hepatitis-c.

54. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin. N Engl J Med. 2014 Apr 10.

55. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med. 2014 Apr 11.

56. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-Ombitasvir and Dasabuvir with or without Ribavirin for HCV. N Engl J Med. 2014 May 4.

57. AbbVie Submits New Drug Application to U.S. FDA for its Investigational, All-Oral, Interferon-Free Therapy for the Treatment of Hepatitis C. [Web Page]: AbbVie; [updated April 22, 2014; cited 2014 May 30]; Available from: http://abbvie.mediaroom.com/2014-04-22-AbbVie-Submits-New-Drug-Application-to-U-S-FDA-for-its-Investigational-All-Oral-Interferon-Free-Therapy-for-the-Treatment-of-Hepatitis-C.

58. Myers RP, Ramji A, Bilodeau M, Wong S, Feld JJ. An update on the management of hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol. 2012 Jun;26(6):359-75.

59. Johnson M, Borland J, Chen S, Song I, Savina P, Wynne B, et al., editors. The effect of boceprevir and telaprevir on dolutegravir pharmacokinetics, in healthy adult subjects. (Abstract O-16). Program and Abstracts of the 14th International Workshop on Clinical Pharmacology of HIV Therapy; 2013 April 22-24; Amsterdam, The Netherlands.

60. ViiV Healthcare ULC. Tivicay (dolutegravir) Prescribing Information. Research Triangle Park, NC2013.

61. Custodio J, Guo S, Lawson EB, Cao H, Silva A, Kearney BP, et al., editors. Lack of clinically relevant drug Interactions between elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate and telaprevir. (Abstract A-1576). 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2013 September 10-13; Denver, CO.

62. Ouwerkerk-Mahadevan S, Simion A, Peeters M, Beumont-Mauviel M, editors. Summary of pharmacokinetic drug-drug interactions for simeprevir (TMC435), a hepatitis C virus NS3/4A protease inhibitor. (Abstract PE 10/7). Program and Abstracts of the 14th European AIDS Conference (EACS); 2013 October 16-19; Brussels, Belgium.

63. de Kanter C, Blonk M, Colbers A, Schouwenberg B, Burger D. Lack of a clinically significant drug-drug interaction in healthy volunteers between the hepatitis C virus protease inhibitor boceprevir and the HIV integrase inhibitor raltegravir. Clin Infec Dis. 2013;56(2):300-6.

64. Van Heeswijk R, Garg V, Boogaerts G, Vandebosch A, Vandevoorde A, Witek J, et al., editors. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers. (Abstract A1-1738a). Abstracts and Proceedings of the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2011 September 17-20; Chicago, IL.

65. Ouwerkerk-Mahadevan S, Sekar V, Peeters M, Beumont-Mauviel M, editors. The pharmokinetic interactions of HCV protease inhibitor TMC435 with rilpivirine, tenofovir, efavirenz or raltegravir in healthy volunteers. (Abstract 49). Program and Abstracts of the 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5-8; Seattle, WA.

66. Kirby B, Mathias A, Rossi S, Moyer C, Shen G, Kearney BP, editors. No clinically significant pharmacokinetic interactions between sofosbuvir (GS-7977) and HIV antiretrovirals Atripla, rilpivirine, darunavir/ritonavir, or raltegravir in

healthy volunteers. (Abstract 1877). Program and Abstracts of the 63rd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD); 2012 November 9-13; Boston, MA.

67. Kasserra C, Hughes E, Treitel M, Gupta S, O'Mara E, editors. Clinical pharmacology of boceprevir: metabolism, excretion, and drug-drug interactions. (Abstract 118). Program and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections; 2011 Feb 27-Mar 2; Boston, MA.

68. Merck Canada Inc. Victrelis (boceprevir) Product Monograph. Kirkland, QC2013.

69. Garg V, Chandorkar G, Yang Y, Adda N, McNair L, Alves K, et al., editors. The effect of CYP3A inhibitors and inducers on the pharmacokinetics of telaprevir [abstract PK_13]. Program and Abstracts of the 6th International Workshop on Clinical Pharmacology of Hepatitis Therapy; 2011 June 22-23; Cambridge, MA.

70. Van Heeswijk R, Vandevoorde A, Boogaerts G, Vangeneugden T, De Paepe E, Polo R, et al., editors. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor TVR in healthy volunteers. (Abstract 119). Abstracts and Proceedings of the18th Conference on Retroviruses and Opportunistic Infections; 2011 Feb 27-Mar 2; Boston, MA.

71. Hammond K, Wolfe P, Burton J, Predhomme J, Ellis C, Ray M, et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers. J Acq Immune Def Syndr. 2013;62(1):67-73.

72. Kakuda TN, Leopold L, Nijs S, Vandevoorde A, Crauwels HM, Bertelsen K, et al., editors. Pharmacokinetic interaction between etravirine or rilpivirine and telaprevir: a randomised, two-way crossover trial. (Abstract O-18). Program and Abstracts of the 13th International Workshop on Clinical Pharmacology of HIV Therapy; 2012 April 16-18; Barcelona, Spain.

73. Rhee E, Feng H-P, Xuan F, Lin WH, Smith C, Zhu Y, et al., editors. Absence of a significant pharmacokinetic interaction between the hepatitis C virus protease inhibitor boceprevir and HIV-1 NNRTI rilpivirine. (Abstract 537). Abstracts and Proceedings of the 20th Conference on Retroviruses and Opportunistic Infections (CROI); 2013 March 3-6; Atlanta, GA.

74. Hulskotte EGJ, Feng H-P, Xuan F, van Zutven M, Treitel M, Hughes E, et al. Pharmacokinetic interactions between the hepatitis C virus protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, darunavir, and lopinavir. Clin Infec Dis. 2013;56(5):718-26.

75. Vertex Pharmaceuticals Inc. Incivek (telaprevir) Product Monograph. Laval, QC2013.

76. AbbVie Corporation. Kaletra (lopinavir/ritonavir) Prescribing Information. Saint Laurent, Canada2012.

77. Vourvahis M, Plotka A, Kantaridis C, Fang A, Heera J. The effects of boceprevir and telaprevir on the pharmacokinetics of maraviroc: An open-label, fixed-

sequence study in healthy volunteers. J Acquir Immune Defic Syndr. 2014;65(5):564-70.

78. Martel D, Sheehan N, Tremblay C, Turgeon J, Tseng A, Phaneuf D, et al., editors. Pharmacokinetic interaction of the directly acting antiviral agent boceprevir and maraviroc in healthy volunteers. (Abstract P-04). Program and Abstracts of the 14th International Workshop on Clinical Pharmacology of HIV Therapy; 2013 April 22-24; Amsterdam, The Netherlands.

79. Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med. 2003 Sep 16;139(6):493-8.

80. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Oct;54(4):1433-44.

Table 1. Virologic response definitions while on HCV therapy

Definition	Time Point	HCV RNA level	Comment
RVR	Week 4	Undetectable	High positive predictive value for SVR
EVR	Week 12	Undetectable: *Complete EVR* Detectable: *Partial EVR* $\geq$2 $\log_{10}$ drop from baseline Detectable: *Null Responder* <2 $\log_{10}$ drop from baseline	Lack of EVR has very high (>98%) negative predictive value for SVR.
eRVR	Week 4, 12	Undetectable	High positive predictive value for SVR with telaprevir-and simeprevir based triple therapy
Partial Response	Week 12+	Partial EVR at week 12 with no subsequent negative HCV RNA test	Treatment failure (pEVR + week 24 HCV RNA detectable, has 100% NPV for SVR)
EOT Response	treatment completion (number of weeks, varies by regimen)	Undetectable	
Relapser	any time after EOT (usually checked 12 or 24 weeks after EOT)	Undetectable at EOT, Detectable after EOT	Treatment Failure (relapse > 12 weeks after EOT suggests possibility of re-infection; viral sequencing should be considered)
SVR 12	Week 60	Undetectable	Predicts SVR24 in mono-infected patients
SVR 24	Week 72	Undetectable	Treatment Success

RVR: rapid virologic response; SVR: sustained virologic response; EVR: early virologic response; eRVR: extended rapid virologic response; pEVR: partial early virologic response; NPV: negative predictive value ; EOT: end of treatment

Table 2. Drug-drug interactions between antiretroviral agents and directly acting antivirals for hepatitis C

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
Dose	800 mg q8h with food	1125mg q12h with food (not low fat)	150 mg daily with food	400 mg daily
Integrase Inhibitors				
Dolutegravir	No clinically significant changes in either drug. No dose adjustment required(59, 60)	No clinically significant changes in either drug. No dose adjustment required.(59, 60)	Co-administration has not been studied but no expected clinically significant drug interaction	Co-administration has not been studied but no expected clinically significant drug interaction
Elvitegravir/ cobicistat	Co-administration has not been studied but co-administration could potentially lead to reduced drug concentrations of both boceprevir and elvitegravir/cobicistat	No clinically significant changes in either drug. No dose adjustment required.(61)	Not recommended with cobicistat-boosted regimens due to risk of significantly increased simeprevir concentrations.(20, 62)	Co-administration has not been studied but no expected clinically significant drug interaction
Raltegravir	No clinically significant changes in either drug. No dose adjustment required.(63)	No clinically significant changes in either drug. No dose adjustment required.(64)	No clinically significant changes in either drug. No dose adjustment required.(65)	No clinically significant changes in either drug. No dose adjustment required.(20, 66)
Non-Nucleoside Reverse Transcriptase Inhibitors				
Efavirenz	44% ↓ Cmin, 19% ↓ AUC of boceprevir. **Avoid combination.**(67, 68)	47% ↓ Cmin of telaprevir; ↑ telaprevir dose to 1125 mg q8h with efavirenz(69, 70)	91% ↓ Cmin, 71% ↓ AUC of simeprevir. **Avoid combination** (20, 62)	6% ↓AUC, 19% ↓ Cmax of sofosbuvir, not considered clinically significant. No dose adjustment required.(20, 66)
Etravirine	29% ↓ Cmin, 23% ↓ AUC of etravirine. Use combination with caution, particularly if coadministering with	No clinically significant changes in either drug. No dose adjustment required.(72)	**Not recommended** with etravirine due to risk of decreased simeprevir concentrations.(20)	Co-administration has not been studied but no expected clinically significant drug interaction

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
	other medications which may further decrease etravirine concentrations (71)			
Rilpivirine	↑ 39% AUC, ↑ 15% Cmax, ↑ 10% Cmin of rilpivirine, not considered clinically significant. No dose adjustment required.(73)	↑ 78% AUC, ↑ 49% Cmax, ↑ 93% Cmin of rilpivirine, not considered clinically significant. No dose adjustment required.(72)	6% ↑ AUC, 4% ↓ Cmin of simeprevir and 12%↑ AUC 25% ↑ Cmin of rilpivirine, not considered clinically significant. No dose adjustment required.(65)	6% ↑ AUC, 5% ↑ Cmax of rilpivirine, not considered clinically significant. No dose adjustment required.(20, 66)
Protease Inhibitors				
Atazanavir/ ritonavir	49% ↓ Ctrough, 35% ↓ AUC of atazanavir. **Avoid combination.**(68, 74)	85% ↑ Cmin of atazanavir. Combination may be used.(70)	**Not recommended** with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations.(20)	No expected clinically significant drug interaction
Darunavir/ ritonavir	59% ↓ Ctrough, 44% ↓ AUC of darunavir and 32% ↓ boceprevir. **Avoid combination.**(68, 74)	40% ↓ AUC and 42% ↓ Cmin of darunavir, 35% ↓ AUC and 32% ↓ Cmin of telaprevir. **Avoid combination.**(70, 75)	2.6-fold ↑ AUC, 1.79-fold ↑ Cmax, 4.58-fold ↑ Cmin of simeprevir and 18% ↑ AUC, 31% ↑ Cmin of darunavir. **Coadministration not recommended**.(20)	37% ↑ AUC, 45% ↑ Cmax of sofosbuvir, not considered clinically significant. No dose adjustment required.(20, 66)
Fosamprenavir/ ritonavir	**Not recommended** with ritonavir-boosted protease inhibitors.(68)	47% ↓ AUC and 56% ↓ Cmin of amprenavir, 32% ↓ AUC and 30% ↓ Cmin of telaprevir **Avoid combination.**(70, 75)	**Not recommended** with ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations.(20, 62)	Co-administration has not been studied but no expected clinically significant drug interaction
Lopinavir/ ritonavir	43% ↓ Ctrough, 34% ↓	6% ↑ AUC and 14% ↑	**Not recommended** with	Co-administration has

	Boceprevir	Telaprevir	Simeprevir	Sofosbuvir
	AUC of lopinavir and 45% ↓ boceprevir. **Avoid combination.**(68, 74, 76)	Cmin of lopinavir, 54 ↓ AUC and 52↓ Cmin of telaprevir. **Avoid combination.**(70, 75, 76)	ritonavir, boosted or unboosted HIV protease inhibitors due to risk of significantly increased simeprevir concentrations.(20)	not been studied but no expected clinically significant drug interaction
CCR5 Antagonist				
Maraviroc	Maraviroc AUC ↑ 202%, Cmax ↑ 233% and Ctrough ↑ 178% vs. maraviroc 150 mg BID alone. **Reduce maraviroc dose to 150 mg BID when coadministering with boceprevir.**(77, 78)	Maraviroc AUC ↑ 849%, Cmax ↑ 681% and Ctrough ↑ 917% vs. maraviroc 150 mg BID alone. **Reduce maraviroc dose to 150 mg BID when coadministering with telaprevir.**(77)	No expected clinically significant drug interaction	Co-administration has not been studied but no expected clinically significant drug interaction

Key: = avoid combination = caution/dose adjustment = combination OK

Q8H: every 8 hours; po: orally; Cmin: concentration minimum; AUC: area under the curve; Cmax: concentration maximum; Ctrough: concentration trough; BID: twice a day

Table 3. Summary of Antiretroviral Regimen Recommendations for Patients Who Require Concomitant HIV and Hepatitis C Treatment.

	Recommended	Alternative	NOT Recommended
Sofosbuvir 400 mg daily	No restrictions on antiretroviral choices.	No restrictions on antiretroviral choices.	
Simeprevir 150 mg daily with food	Dolutegravir, raltegravir, or rilpivirine-based regimens.		Ritonavir- or cobicistat-boosted regimens; efavirenz, etravirine, nevirapine
Telaprevir 1125mg BID with food (not low fat)	Atazanavir/ritonavir, dolutegravir, elvitegravir, raltegravir, or rilpivirine-based regimens.	Efavirenz (with increase in telaprevir dose to 1125 mg q8h), etravirine.	Other Protease Inhibitor-based regimens, including: Darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir.
Boceprevir 800 mg q8h with food	Dolutegravir, raltegravir, or rilpivirine-based regimens.		Protease Inhibitor based regimens including: Atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir; Other NNRTI-based regimens including: efavirenz, etravirine, nevirapine

BID: twice daily; Q8h: every 8 hours

NNRTI: non-nucleoside reverse transcriptase inhibitors

Appendix

Table Grading system for recommendations

Classification Description	
Class of Evidence	
Class 1	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial , useful and effective
Class 2	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure or treatment
Class 2a	Weight of evidence/opinion is in favour of usefulness/efficacy
Class 2b	Usefulness /efficacy is less well established by evidence/opinion
Class 3	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure/treatment is not useful/effective and in some cases may be harmful
Grade of Evidence	
Level A	Data derives from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Only consensus opinions of experts, case studies, or standard-of-care.

Adapted from (58, 79, 80)