Court File No. 98-CV-141369 CP00

ONTARIO
SUPERIOR COURT OF JUSTICE

B E T W E E N :

DIANNA LOUISE PARSONS, MICHAEL HERBERT CRUICKSHANKS, DAVID TULL, MARTIN HENRY GRIFFEN, ANNA KARDISH, ELSIE KOTYK, Executrix of the Estate of Harry Kotyk, deceased and ELSIE KOTYK, personally

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY,
HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO
and THE ATTORNEY GENERAL OF CANADA

Defendants

and

HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF ALBERTA
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF SASKATCHEWAN,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF MANITOBA,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEW BRUNSWICK
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF PRINCE EDWARD ISLAND,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NOVA SCOTIA
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEWFOUNDLAND,
THE GOVERNMENT OF THE NORTHWEST TERRITORIES,
THE GOVERNMENT OF NUNAVUT and THE GOVERNMENT OF THE YUKON TERRITORY

Intervenors

Proceeding under the *Class Proceedings Act, 1992*

Court File No. 98-CV-146405

B E T W E E N:

JAMES KREPPNER, BARRY ISAAC, NORMAN LANDRY, as Executor of the Estate of the late SERGE LANDRY, PETER FELSING, DONALD MILLIGAN, ALLAN GRUHLKE, JIM LOVE and PAULINE FOURNIER as Executrix of the Estate of the late PIERRE FOURNIER

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, THE ATTORNEY GENERAL OF CANADA and
HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Defendants

and

HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF ALBERTA,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF SASKATCHEWAN,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF MANITOBA,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEW BRUNSWICK,
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF PRINCE EDWARD ISLAND
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NOVA SCOTIA
HER MAJESTY THE QUEEN IN THE RIGHT OF THE PROVINCE OF NEWFOUNDLAND,
THE GOVERNMENT OF THE NORTHWEST TERRITORIES,
THE GOVERNMENT OF NUNAVUT AND THE GOVERNMENT OF THE YUKON TERRITORY

Intervenors

Proceeding under the *Class Proceedings Act, 1992*

This is the 15th Affidavit
of Heather Rumble Peterson in this case
and was made on 1/Apr/16

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

C A N A D A

PROVINCE OF QUÉBEC

DISTRICT OF MONTRÉAL

NO : 500-06-000016-960

S UPERIOR COURT

Class action

DOMINIQUE HONHON

Plaintiff

-vs-

THE ATTORNEY GENERAL OF CANADA
THE ATTORNEY GENERAL OF QUÉBEC
THE CANADIAN RED CROSS SOCIETY

Defendants

-and-

MICHEL SAVONITTO, in the capacity of the Joint Committee member for the province of Québec

PETITIONER

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

C A N A D A

PROVINCE OF QUÉBEC

DISTRICT OF MONTRÉAL

NO : 500-06-000068-987

SUPERIOR COURT

Class action

DAVID PAGE

Plaintiff

-vs-

THE ATTORNEY GENERAL OF CANADA
THE ATTORNEY GENERAL OF QUÉBEC
THE CANADIAN RED CROSS SOCIETY

Defendants

-and-

FONDS D'AIDE AUX RECOURS COLLECTIFS

-and-

LE CURATEUR PUBLIC DU QUÉBEC

Mis-en-cause

AFFIDAVIT OF HEATHER RUMBLE PETERSON
(sworn April 1, 2016)

I, HEATHER RUMBLE PETERSON, of the Town of Harrow, in the County of Essex, lawyer, MAKE OATH AND SAY:

1. I am a partner at Sutts, Strosberg LLP. I previously swore an affidavit dated October 16, 2015, in support of the Joint Committee's application to have actuarially unallocated assets designated to Class and Family Class Members. In brief, I participated with Harvey T. Strosberg and other members of the Ontario counsel group in litigating the Ontario transfused action from the outset and have the day-to-day responsibility at my firm to manage and supervise administration of the 1986-1990 Hepatitis C Settlement Agreement. As such, I have knowledge of the facts to which I depose in this affidavit. Where I make statements in this affidavit which are not within my personal knowledge, I have identified the source of that information. I do verily believe all of the facts and information to which I depose herein to be true.

Class Members Have Borne the Costs Associated With the Trust Fund

2. After the Agreement in Principle was reached in December 1998 and well into the negotiation of the form of the settlement and funding agreements, in May 1999, the governments sought changes to the way settlement funds would be held and advanced which were unacceptable to class counsel. These issues were resolved by agreement that the federal government would pay its share of the settlement amount into a Trust, the assets of which would be held by the Trustee for the benefit of the class

members and other persons entitled to be paid out of the Trust, and operated in accordance with a structure provided for in the Settlement and Funding Agreements. For ease of reference, annexed as **Exhibit "A",** is Mr. Strosberg's letter of May 5, 1999 which is also found as part of the federal government's application material at Exhibit "O" to the affidavit of Asvini Krishnamoorthy sworn January 29, 2016.

3. To properly implement, settle and manage the Trust a structure was required. This included development of Terms of Appointment of a Trustee, Investment Manager and Investment Consultant as well as Investment Guidelines and administrative procedures permitting the Administrator to call on the funds to meet the liabilities to the class members, family class members and service providers as required.

4. William Mercer was retained to provide advice and assistance with the development of the Investment Guidelines and the various Terms of Appointment. These costs in the amount of $73,016 were incurred by Class Counsel in the first instance, but reimbursed from settlement funds when the Courts approved fees and disbursements. Annexed as **Exhibit "B"** is a copy of the Mercer Accounts.

5. Along with approval of the Settlement and Funding Agreements and the Investment Guidelines and Terms of Appointment, Royal Trust Company was appointed Trustee, TD Asset Management Inc. was appointed Investment Manager, Towers Perrin was appointed Investment Consultant and Deloitte & Touche was appointed Auditor of the Trust. Start-up costs associated with setting up the trust and administrative procedures were paid from the settlement funds as follows:

Royal Trust	$40,089
TD Asset	$60,925
Towers Perrin	$19,368
Deloitte	$39,013
TOTAL	**$159,395**

Annexed as **Exhibit "C"** is the May 10, 2000 Order made by the Ontario Court in respect of these costs. Complimentary orders were made in each of the other jurisdictions.

6. The Administrator also incurred start-up costs in the amount of $305,072 paid from the settlement funds. A portion of these costs were related to establishing the payment structure and procedures necessitated by the Trust. Annexed as **Exhibit "D"** is a copy of the May 10, 2000 Order made by the Ontario Court in respect of these costs. Complimentary orders were also made in each of the other jurisdictions.

7. There have been significant ongoing costs associated with the requirements to maintain the Trust structure and to administer the Plans. Annexed as **Exhibit "E"** is a chart I have compiled from information contained in the Joint Committee's various Annual Reports to the Courts covering the period from January 1, 2000 to December 31, 2013. All of these costs have been paid from the settlement funds.

8. This chart is by no means an exhaustive list of all of the costs borne by the Trust or the class pertaining to the settlement. The service providers included in this chart are however in my view those most closely associated with operating the Trust and administering the settlement.

9. There are other aspects of the operation of the Plans and costs that the Joint Committee did not oversee or that were not as obviously tied to the Trust and/or direct administration, such as the Monitor, the Referees and Arbitrators and Canadian Blood Services and Hema Quebec which I have not included in the chart.

10. It was a fundamental term of the Settlement and Funding Agreements that the settlement amount paid by the federal government and the settlement amount payable by the provincial and territorial governments were the totality of the amounts payable under the settlement:

> 4.03 No Additional Liability
>
> … For greater certainty, none of the FPT Governments will be liable to provide any additional funds if the amount of funds to be provided by the FPT Governments pursuant to this Article Four and the Funding Agreement are insufficient to make all the payments to be made pursuant to this Agreement including, for greater certainty, the Plans and the Funding Agreement.

11. Accordingly, the Class Members and the Family Class Members have borne all of the cost over the course of these 14 years of administration to the December 31, 2013 valuation date as well as the risk of insufficiency of the Trust Fund and will continue to do so until such time as the Settlement Agreement is terminated in accordance with its terms.

Compensable HCV Drug Therapy and the Transition from Disease Level 2 to Disease Level 3

12. On October 16, 2015, the Joint Committee served applications requesting that the Courts declare: that the amount of Excess Capital available for allocation is a

lesser amount than originally determined, namely, $206,920,000; allocate approximately $205.4 million of the Excess Capital for the benefit of Class Members and Family Class Members; and retain the remaining Excess Capital within the Trust Fund.

13. The basis of the request for a reduction in Excess Capital was a belief on the part of the Joint Committee that an additional sufficiency liability in respect of Disease Level 2 claimants who are reclassified as Disease Level 3 claimants and become eligible for the $30,000 ($1999) Level 3 fixed payment based on meeting a protocol for Compensable HCV Drug Therapy should be reflected in the financial position of the Trust. While the medical model provides for a Level 2 to Level 3 transition based on disease progression, it does not account for this Disease Level transition based on the protocol.

14. The federal government served its application and responding material including an affidavit of Peter Gorham attaching the Morneau Shepell *Actuarial Report on Proposed Allocation of the Actuarially Unallocated Funds as of 31 December 2013.* In that report, Mr. Gorham raises the issue of the appropriateness of a Disease Level 2 to Disease Level 3 transition "by reason only of taking the new treatment... ." Mr. Gorham suggests in his report that "the situation be reviewed to determine whether the court approved protocol regarding these payments should be revised."

15. Since the appropriateness of this payment has been raised, the Joint Committee has instructed the Administrator to refrain from approving class members for Disease Level 3 based upon Compensable HCV Drug Therapy unless interferon or

ribavirin are part of their course of treatment until this issue can be resolved by the Parties or the Courts.

16. I set out information relevant to this issue below.

17. The Plans provide for fixed payments to Class Members based upon criteria associated with their disease progression. A fixed payment in the amount of $30,000 is payable at Disease Level 3 pursuant to section 4.01(1)(c) of the Plans as follows:

> …upon delivering to the Administrator evidence demonstrating that he or she has (i) developed fibrous tissue in the portal areas of the liver with fibrous bands extending out from the portal area but without any bridging to other portal tracts or to central veins (i.e., non-bridging fibrous) or (ii) received Compensable HCV Drug Therapy or (iii) has met or meets a protocol for Compensable HCV Drug Therapy notwithstanding that such treatment was not recommended, or if recommended, has been declined;

18. Compensable HCV Drug Therapy is defined under the Plans as follows:

> "Compensable HCV Drug Therapy" means interferon or ribavirin, used alone or in combination, or any other treatment that has a propensity to cause adverse side effects and that has been approved by the Courts for compensation.

19. A protocol developed by the Joint Committee in consultation with medical experts and approved by the Courts entitled – *Medical Evidence for Section 4.01(1) and Section 4.01(2) of Article 4 the Transfused HCV Plan and the Hemophiliac HCV Plan* is annexed as **Exhibit "F"**. It provides instruction to the Administrator in respect of evidence acceptable for the various disease level approvals including for Disease Level 3.

20. The Administrator in consultation with the Joint Committee also developed various forms for completion by Class Members and/or their Treating Physicians to establish various entitlements under the Plans including Treating Physician Form 2 relating to identification of the Class Member's appropriate disease level. This is the form that the Administrator requires to assess, among other things, whether a class member has reached Disease Level 3. Annexed as **"Exhibit G"** is the Treating Physician Form 2.

21. The court approved protocol on medical evidence and the Treating Physician Form 2 each reference the Canadian Association for the Study of the Liver (CASL) Consensus Guidelines as one of the criteria pertaining to the Disease Level 3 determination. The CASL Consensus Guidelines in place from January 1, 2012 are annexed as **Exhibit "H"**. In January or February 2015 a new set of CASL Guidelines were developed and published. The current CASL Consensus Guidelines are annexed as **Exhibit "I"**.

22. Kevin O'Connell the Senior Project Manager for the Administrator has advised me that there have been 150 Disease Level 3 approvals made since January 1, 2012 as follows:

(a) 30 class members were approved at Disease Level 3 under provision (a) in the protocol – developed non-bridging fibrosis;

(b) 34 class members were approved at Disease Level 3 under provision (b) in the protocol – undergone Compensable HCV Drug Therapy;

(c) 7 class members were approved at Disease Level 3 under provision (c) in the protocol – doctor certification they met the outlined protocol for Compensable HVC Drug Therapy i.e., elevated ALTs etc.; and

(d) 79 class members were approved at Disease Level 3 under provision (d) in the protocol – doctor certification they met the protocol for Compensable HCV Drug Therapy consistent with the treatment decision factors set out in the most recent CASL Consensus Guidelines.

23. Annexed as **Exhibit "J"** is a spreadsheet which provides additional information concerning the 7 claimants approved under provision (c) of the protocol - doctor certification they met the outlined protocol for Compensable HVC Drug Therapy i.e., elevated ALTs etc..

24. Annexed as **Exhibit "K"** is a spreadsheet which provides additional information concerning the 79 claimants approved under provision (d) of the protocol - doctor certification they met the protocol for Compensable HCV Drug Therapy consistent with the treatment decision factors set out in the most recent CASL Consensus Guidelines.

25. Mr. Gorham also discusses the $1000 per month payment for class members who take Compensable HCV Drug Therapy in these same sections of his report. I am advised by Mr. O'Connell that payments are only made under this provision if the class member is in fact taking/has taken Compensable HCV Drug Therapy ie. interferon or ribavirin, alone or in combination as provided in the Plans.

The Joint Committee's Recommended Allocation of Excess Capital

26. I am advised by Richard Border that the 10% lost pension benefit calculation at page 19 section A.3 of the Eckler report entitled *Proposed Allocation of*

the 2013 Sufficiency Assessment Actuarially Unallocated Assets only applies to loss of income payments and not to loss of support payments. The Joint Committee intends to serve amended applications which will provide for this along with the materials it is filing in response to the federal government's applications.

SWORN BEFORE ME at the City of Windsor, in the County of Essex, this 1st day of April, 2016.

Commissioner for taking affidavits
1400683

Shelley Lynn Woodrich, a Commissioner, etc., County of Essex, for Sutts, Strosberg LLP, Barristers and Solicitors. Expires February 18, 2019.

HEATHER RUMBLE PETERSON

THE ATTACHED IS EXHIBIT "A" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

GIGNAC, SUTTS
BARRISTERS & SOLICITORS

COUNSEL
HARVEY T. STROSBERG, Q.C.

TELEPHONE
(519) 258-9333
(800) 229-5323
FAX
(519) 258-9527

E-MAIL
hep-c@gignacsutts.com

OUR FILE NO 44-900-000

MAILING ADDRESS
P.O. BOX 670
251 GOYEAU STREET
WINDSOR, ONTARIO, CANADA
N9A 6V4

HARVEY T. STROSBERG, Q.C.
E-mail: hts-sc@gignacsutts.com
Direct Dial (519) 561-6228
Direct Fax (519) 258-9503

This is Exhibit "LLL" referred to in the affidavit of JJ Camp made before me on MAY 27 19 99

A Commissioner for taking Affidavits For British Columbia

May 5, 1999

VIA FACSIMILE

VIA FAX ONLY TO

NAME:	Ivan G. Whitehall		
FAX:	613-952-8713		
PHONE:	613-957-4801		
NAME:	Clifton D. Prowse		
FAX:	604-660-2636		
PHONE:	604-660-3091		
PGS:	4	TIME:	AM / PM

This message is intended for the use of the individual(s) to which it is addressed and may contain information that is privileged and confidential. If you are not the intended recipient, or the employee or agent responsible for delivering the message to the intended recipient, any dissemination, distribution or copy is prohibited. If you have received this communication in error, please destroy it and notify us by telephone immediately.

Ivan G. Whitehall, Q.C.
Room 2341
284 Wellington Street
East Memorial Building
Ottawa, Ontario K1A 0H8
Canada

Mr Clifton D. Prowse
British Columbia Ministry of the
Attorney General
Legal Services Branch
1301-865 Howe Street
Vancouver, BC V6Z 2H4

Dear Sirs:

Parsons et al. v. The Canadian Red Cross Society
Court File No.: 98-CV-141369

I have now had an opportunity to consider the documents which were faxed to us on Thursday, April 29.

I begin by reciting history. We agreed in the "Framework Agreement" that the $1,118,000,000 would attract monthly interest at the long-term Government of Canada bond rate.

Mr. Whitehall explained at our meeting at McCarthy Tetrault that the FPT Governments would hold the $1,118,000,000 and wished to invest by purchasing Three Month Federal Government Treasury Bills ("T-bills"), a readily accessible investment, to match T-bill rates which it wished to pay instead of the long-term Government of Canada bond rate. This seemed

reasonable to me because the FPT Governments were to hold the monies.

I told Mr. Whitehall that (subject to court approval) I would accept three month T-bill rates and interest compounded quarterly if all other terms were as we had proposed. This concession had a value of 75 to 125 basis points per year.

Since then the following evolution has occurred in your drafts:

(a) a trustee has been proposed to hold the settlement monies;

(b) the FPT Governments reserve to themselves the right to earn a spread on the settlement monies by investing in bonds or otherwise directing investment policy;

(c) some costs of administration are to be passed to the victims' fund;

(d) the scope of the release form has been substantially expanded;

(e) an indemnity is sought from victims relating to family claims;

(f) the right to appeal quantum from a referee's decision has been eliminated;

(g) there is no fixed percentage to be paid by any FPT Government raising the prospect of several liability for an unascertained amount;

(h) no FPT Government has given a covenant to pay a fixed amount to the victim because they are not parties to the Funding Agreement; and

(i) a Funding Agreement has been produced that is so convoluted and complex as to be a recipe for costly litigation (if the victims were in a position to enforce it).

This approach is utterly unacceptable and represents an unwarranted dilution of the terms necessary for counsel's recommendation and court approval.

Given the passage of time and the variation in the FPT Governments' position, I am not prepared to accept the Funding Agreement.

I propose the following approach:

1. The FPT Governments will, in the Settlement Agreement, convenant to pay $1,118,000,000 plus interest from April 1, 1998 to the date of payment to the Trustee at the three month T-bill rates compounded quarterly less expenses ("Settlement Amount").

2. The Federal Government will pay forthwith upon Court approval, 72.7273% of the Settlement Amount to a Trustee appointed by the Courts.

3. The Provincial and Territorial Governments will agree on a fixed percentage of the balance of the Settlement Amount to be paid by each Government to the Trustee and each Government will guarantee only the fixed percentage attributed to it.

4. The Trustee, on the direction of investment managers approved by the Courts, will invest the monies it has on hand. Whatever interest accrues will become part of the Settlement Amount. This will create a yield for the victims in excess of the T-bill rate.

5. Any Provincial or Territorial Government which cannot or will not pay their share immediately will be charged interest at the T-bill rate to be compounded and accrued or paid to the Trustee quarterly. I understood that Ontario has allocated $130,000,000 more or less. I am hopeful that Premier Harris will ensure that Ontario's percentage is immediately paid over to the Trustee.

6. Monthly, the Administrator, on 10 days' notice, will requisition such monies as it requires. If there is any dispute about the reasonableness of the requisition, a motion may be made to any of the courts for advice and directions.

7. How the FPT Governments adjust the payments among themselves is for the FPT Governments and the victims need have no concern with this.

8. There will be no indemnity given in any release. The FPT Governments can be protected by a clause in the Settlement Agreement which provides that if any class member opts out, any

judgment or approved settlement is paid out of the Settlement Amount.

9. There must be the right to appeal quantum from a referee's decision. There is no risk that these appeals will overburden the court system. There are few pending appeals in the Ontario Court of Appeal dealing only with quantum of damages.

Yours very truly,

Harvey T. Strosberg

Harvey T. Strosberg

HTS/ba
cc: Daryl McLean
Fax: (416) 868-0673
Tel: (416) 601-7700
G:\LIT\CLASS\HEPC\64900045.doc

THE ATTACHED IS EXHIBIT "B" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

WILLIAM M. MERCER

Investment Consulting

INVOICE

Invoice Number: 025869324
Invoice Date: 01-Nov-1999
Client Account: HEP130 - 07

Bonnie A. Tough
Barrister & Solicitor
Hodgson Tough Shields DesBrisay O'Donnell
550 -36Toronto Street
TORONTO ON M5C 2C5

For professional services to October 27, 1999		$2,640.00
GST		$184.80
	Total	$2,824.80

GST 871117966R

Please retain this copy for your records

Invoices are due upon receipt.
Overdue invoices are subject to 1.0% per month service charges (equivalent to 12% per annum).

William M. Mercer Limited
P.O. Box 501 161 Bay Street
Toronto, ON M5J 2S5
Tel. 416 868 2000

WILLIAM M MERCER

INVOICE

Investment Consulting

Invoice Number: 025869324
Invoice Date. 01-Nov-1999
Client Account: HEP130 - 07

Bonnie A. Tough
Barrister & Solicitor
Hodgson Tough Shields DesBrisay O'Donnell
550 -36Toronto Street
TORONTO ON M5C 2C5

For professional services to October 27, 1999		$2,640.00
GST		$184.80
	Total	$2,824.80

GST 871117966R

Remittance Copy - Please return this copy with your payment to:

P.O. Box 70133 Station A
TORONTO ON M5W 2X5

Invoices are due upon receipt.
Overdue invoices are subject to 1.0% per month service charges (equivalent to 12% per annum).

William M Mercer Limited
P.O. Box 501 161 Bay Street
Toronto, ON M5J 2S5
Tel: 416 868 2000

WILLIAM M MERCER

Investment Consulting

INVOICE SCHEDULE

Invoice Number : 025869324
Invoice Date: 01-Nov-1999

Client : HEP130 - 07
1986 - 1990 Hepatitis C Settlement

Attention: Bonnie Tough

No	Item	Remark	Amount
1	Investment Consulting	Preparation for and attending in Court as witness on October 21	$2,640.00
		Total	$2,640.00

WILLIAM M. MERCER

Investment Consulting

INVOICE

Invoice Number. 025865353
Invoice Date 11-Aug-1999
Client Account. HEP130 - 07

Bonnie A. Tough
Barrister & Solicitor
Hodgson Tough Shields DesBrisay O'Donnell
550 -36Toronto Street
TORONTO ON M5C 2C5

For professional services to July 28, 1999		$31,100.00
GST		$2,177.00
	Total	$33,277.00

GST 871117966R

Please retain this copy for your records

Invoices are due upon receipt.
Overdue invoices are subject to 1 0% per month service charges (equivalent to 12% per annum).

William M. Mercer Limited
P.O. Box 501 161 Bay Street
Toronto, ON M5J 2S5
Tel: 416 868 2000

WILLIAM M. MERCER

Investment Consulting

INVOICE

Invoice Number: 025865353
Invoice Date: 11-Aug-1999
Client Account: HEP130 - 07

Bonnie A. Tough
Barrister & Solicitor
Hodgson Tough Shields DesBrisay O'Donnell
550 -36Toronto Street
TORONTO ON M5C 2C5

For professional services to July 28, 1999		$31,100.00
GST		$2,177.00
	Total	$33,277.00

GST 871117966R

Remittance Copy - Please return this copy with your payment to.

P.O. Box 70133 Station A
TORONTO ON M5W 2X5

Invoices are due upon receipt
Overdue invoices are subject to 1.0% per month service charges (equivalent to 12% per annum).

William M. Mercer Limited
P.O. Box 501 161 Bay Street
Toronto, ON M5J 2S5
Tel: 416 868 2000

WILLIAM M. MERCER

Investment Consulting

INVOICE SCHEDULE

Invoice Number: 025865353
Invoice Date: 11-Aug-1999

Client: HEP130 - 07
1986 - 1990 Hepatitis C Settlement

Attention: Bonnie Tough

No.	Item	Remark	Amount
1	Investment Consulting	Work in progress on asset mix report	$13,000.00
2	Investment Consulting	Work in progress on investment guidelines	$2,000.00
3	Investment Consulting	Work in progress on custodian search report	$3,000.00
4	Investment Consulting	Work in progress on manager search report	$5,000.00
5	Investment Consulting	Preparation for and attendance at meeting of July 22 with class counsel; Mercer attendees - R. Martin, K. Schaefer	$2,200.00
6	Investment Consulting	Letter of July 23 describing deliverables, timeline, fees	$1,320.00
7	Investment Consulting	Draft summary report on manager and trustee selection process	$700.00
8	Investment Consulting	Preparation for and attendance at meeting of July 27 with class counsel; Mercer attendees - R. Martin, K. Schaefer	$3,880.00
		Total	$31,100.00

WILLIAM M. MERCER

Investment Consulting
Direct 416 868 7085

Private & Confidential

September 13, 1999

Bonnie A. Tough
Specialist in Civil Litigation
Hodgson Tough Shields DesBrisay O'Donnell
Barristers and Solicitors
550 – 36 Toronto Street
Toronto, Ontario
M5C 2C5

Subject: Invoice for Consulting Services - Hepatitis C

Dear Bonnie,

We enclose our invoice in the amount of $34,500 (excluding GST) for professional services rendered as per the attached schedule of services.

Thank you for using our services.

Yours very truly,

Klaus Schaefer

Enclosure

William M. Mercer Limited
BCE Place, 161 Bay Street, P.O. Box 501
Toronto, Ontario M5J 2S5
Tel 416 868 2000
Fax 416 868 2131

WILLIAM M. MERCER

Investment Consulting

INVOICE

Invoice Number 025866519
Invoice Date: 13-Sep-1999
Client Account. HEP130 - 07

Bonnie A. Tough
Barrister & Solicitor
Hodgson Tough Shields DesBrisay O'Donnell
550 -36Toronto Street
TORONTO ON M5C 2C5

For professional services to August 29, 1999		$34,500.00
GST		$2,415.00
	Total	$36,915.00

GST 871117966R

Please retain this copy for your records

Invoices are due upon receipt.
Overdue invoices are subject to 1.0% per month service charges (equivalent to 12% per annum).

William M. Mercer Limited
P.O. Box 501 161 Bay Street
Toronto, ON M5J 2S5
Tel: 416 868 2000

WILLIAM M. MERCER

Investment Consulting

INVOICE

Invoice Number: 025866519
Invoice Date: 13-Sep-1999
Client Account: HEP130 - 07

Bonnie A Tough
Barrister & Solicitor
Hodgson Tough Shields DesBrisay O'Donnell
550 -36Toronto Street
TORONTO ON M5C 2C5

For professional services to August 29, 1999		$34,500.00
GST		$2,415.00
	Total	$36,915.00

GST 871117966R

Remittance Copy - Please return this copy with your payment to:

P.O. Box 70133 Station A
TORONTO ON M5W 2X5

Invoices are due upon receipt.
Overdue invoices are subject to 1.0% per month service charges (equivalent to 12% per annum)

William M Mercer Limited
P.O. Box 501 161 Bay Street
Toronto, ON M5J 2S5
Tel: 416 868 2000

WILLIAM M. MERCER

Investment Consulting

INVOICE SCHEDULE

Invoice Number: 025866519
Invoice Date: 13-Sep-1999

Client: HEP130 - 07
1986 - 1990 Hepatitis C Settlement

Attention: Bonnie Tough

No.	Item	Remark	Amount
1	Investment Consulting	Finalizing asset mix report	$4,900.00
2	Investment Consulting	Finalizing investment guidelines	$6,900.00
3	Investment Consulting	Finalizing custodian search report	$5,500.00
4	Investment Consulting	Finalizing manager search report	$11,500.00
5	Investment Consulting	Finalizing summary report on manager and trustee selection process	$500.00
6	Investment Consulting	Letter of August 10 reviewing Met Life funding proposal	$750.00
7	Investment Consulting	Letters of August 11 and 16 describing ongoing monitoring process and activities	$1,900.00
8	Investment Consulting	Meeting of August 11 with class counsel; Mercer attendee - Klaus Schaefer	$750.00
9	Investment Consulting	Discussions with Quebec class counsel on August 11 and 12, and letter of August 12, concerning miscellaneous investment manager issues	$1,500.00
10	Investment Consulting	Miscellaneous discussions and correspondence	$300.00
		Total	$34,500.00

THE ATTACHED IS EXHIBIT "C" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Court file # 98-CV-141369 CP

ONTARIO
SUPERIOR COURT OF JUSTICE

THE HONOURABLE MR. JUSTICE	)	THURSDAY, THE 10TH DAY
	)	
WARREN K. WINKLER	)	OF MAY, 2000

BETWEEN:

DIANNA LOUISE PARSONS, MICHAEL HERBERT CRUICKSHANKS, DAVID TULL, MARTIN HENRY GRIFFEN, ANNA KARDISH, ELSIE KOTYK, Executrix of the Estate of Harry Kotyk, deceased and ELSIE KOTYK, personally

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO and THE ATTORNEY GENERAL OF CANADA

Defendants

Proceeding under the *Class Proceedings Act, 1992*

Court File No. 98-CV-146405

BETWEEN:

JAMES KREPPNER, BARRY ISAAC, NORMAN LANDRY, as Executor of the Estate of the late SERGE LANDRY, PETER FELSING, DONALD MILLIGAN, ALLAN GRUHLKE, JIM LOVE and PAULINE FOURNIER as Executrix of the Estate of the late PIERRE FOURNIER

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, THE ATTORNEY GENERAL OF CANADA and HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Defendants

Proceeding under the *Class Proceedings Act, 1992*

ORDER

THIS MOTION, made by the representative plaintiffs, was heard this day at Toronto, Ontario.

ON READING the affidavits of Patricia A. Speight, sworn May 1, 2000 and David L. Robins, sworn May 5, 2000,

AND ON HEARING the submissions of counsel for the representative plaintiffs,

1. THIS COURT ORDERS AND DECLARES that since the Ontario Class Actions have been stayed against the CRCS by the order of Mr. Justice Blair made on July 20, 1998 in action no. 98-CL-002970 (Toronto) (the "Stay"), the Stay having been subsequently extended by further orders of the Court made on August 19, 1998, October 5, 1998, January 18, 1999, May 5, 1999, July 28, 1999 and February 25, 2000, nothing in this order is to have the effect of prejudicing the CRCS.

2. THIS COURT ORDERS that the definitions set out in paragraph 2 of the judgment issued on the 22nd day of October, 1999 (the "October 22, 1999 judgment") apply to this order.

3. THIS COURT ORDERS that the response of Gamma-Dynacare Medical Laboratories ("Dynacare"), attached hereto as Schedule 1, to the request for proposal for

PCR testing, attached hereto as Schedule 2, be and the same is hereby accepted and Dynacare is appointed to perform PCR testing for the purposes of the Plans.

4. THIS COURT ORDERS that the Administrator liaise with Dynacare to put in place PCR testing across Canada.

5. THIS COURT ORDERS that Royal Trust Company shall pay the following persons the following amounts which the court considers appropriate for services rendered to March 31, 2000:

Person	Position	Amount
Royal Trust Company	Trustee of the Trust	$40,089.00
TD Asset Management	Investment Manager	$60,925.92
Towers Perrin	Investment Consultant	$19,368.00
Deloitte & Touche	Auditor	$39,013.54
Eckler Partners	Actuary	$4,782.90

6. THIS COURT ORDERS that Royal Trust Company shall pay the following persons the following amounts which the court considers appropriate as their monthly budget payment from and after April 1, 2000 for the term of their appointment, or until further order of the Courts:

Person	Position	Monthly Budget Payment
Royal Trust Company	Trustee of the Trust	$13,917.00
TD Asset Management	Investment Manager	$21,917.00
Towers Perrin	Investment Consultant	$4,667.00
Deloitte & Touche	Auditor	$3,750.00
Eckler Partners	Actuary	$3,000.00

7. THIS COURT ORDERS that Royal Trust Company, TD Asset Management Inc., Towers Perrin, Deloitte & Touche and Eckler Partners shall at least annually present their accounts for services rendered to the Courts for approval and account for the monthly budget payments received by them.

8. THIS COURT DECLARES that the payments particularized in this order shall not be made by Royal Trust Company until they are also authorized by the courts of British Columbia and Quebec.

9. THIS COURT ORDERS that this order shall be issued, entered and then filed in the Ontario Transfused Class Action Court file numbered 98-CV-141369 and the Ontario Hemophiliac Class Action Court file numbered 98-CV-146405.

ENTERED AT/INSCRIT À TORONTO
ON/BOOK NO:
LE/DANS LE REGISTRE NO.:

JUN 2 1 2000

AS DOCUMENT NO.:
À TITRE DE DOCUMENT NO.:
PER/PAR:

JUSTICE

G:\LIT\CLASS\Hepc\Pleadings\order-051000(3).doc

April 28, 2000

RESPONSE TO REQUEST FOR PROPOSAL DATED APRIL 17, 2000, RE: HEPATITIS C 1986-1990 CLASS ACTION SETTLEMENT

1. BACKGROUND

Gamma-Dynacare Medical Laboratories (GD) is a medical laboratory licensed by the Ontario Ministry of Health and Long Term Care. GD is accredited by the College of American Pathologists (CAP), which is the regulatory body for medical laboratories in the United States. Aside from our own internal quality control (QC) programs, GD also utilizes external QC programs and participates in the proficiency programs of the Ontario Medical Association (the Laboratory Proficiency Testing Program) and CAP.

GD operates three major, wholly owned laboratories in the Province of Ontario (Brampton, Ottawa and London) as well as twenty-eight additional smaller laboratories in the Province. A partnership agreement for ownership and operation of the laboratories at Sunnybrook and Women's College Health Sciences Centre has been in effect for almost five years. In addition, an "agreement in principle" exists for the construction and management of a regional laboratory serving the Ottawa Hospital system as well as the other hospitals in the Eastern Ontario region.

The Brampton laboratory at GD is the largest laboratory in Canada, occupying in excess of 75,000 square feet and processing specimens from approximately 17,000 patients per day. These "patients" include both routine medical patients as well as specimens from "industrial accounts" and clinical trial specimens.

Aside from the Ontario operations, GD owns a majority interest in and is the operating partner of Dynacare-Kasper Medical laboratories (DKML) in Edmonton, Alberta. DKML performs all of the community laboratory testing in the region for the Capital Health Authority. In addition, DKML operates all of the hospital laboratories in the Edmonton region (with the exception of the University Hospital laboratory). DKML has extensive experience in clinical trial coordination, shipping and testing.

Dynacare owns and operates two of the three SAMHSA-accredited drug-testing laboratories in Canada (in London, Ontario and at DKML). As such, we routinely perform chain-of-custody collections and ship such specimens across Canada. A full cross-Canada network of collection centres are already in routine use by GD and it is suggested that they be used for this project as well. The GD coordinator will, where possible, direct patients to one of these collection centres for specimen collection.

In the United States, Dynacare operates more than twenty laboratories. These are either wholly owned reference laboratories, laboratories owned and operated in partnership with major hospitals or community laboratories owned in partnership with pathology groups.

In terms of gross sales, Dynacare is the third largest medical laboratory system in North America after Quest/Smith-Kline and Labcorp of America.

2. LOGISTICS

We envision the program will be set up as follows:

GD will appoint a program coordinator for this project. A 1-800 toll free number will be available for use by people wishing to be tested for Hepatitis C by PCR. There will be a bilingual, recorded message on that line by which each patient will be greeted and informed that "this is the correct number to call to arrange a PCR test for Hepatitis C". Patients will be asked to leave their name and telephone number with the message centre and will assure them that all information will be kept confidential. The coordinator will then call these people and arrange an appointment with them to either visit a local specimen collection centre or, if they cannot travel to one, to have a nurse visit their home for specimen procurement.

The GD project coordinator will answer questions they may have regarding the procurement or type of specimens. However for questions regarding the interpretation of the test results or for interpretation of the Hepatitis C testing program etc., they will be referred to the program administrator.

Results will be given only to the program administrator unless we are otherwise informed. Reporting of patient results will maintain patient confidentiality as is the routine procedure for this laboratory. Turnaround time for results will vary depending upon testing load however we anticipate a turnaround time of no longer than two weeks at any time.

3. TRAINING, COLLECTION, SHIPPING AND STORAGE

Training: A collection manual will be prepared and sent to all locations and personnel who will be involved in the procurement and/or shipping of specimens in this program. This manual will contain in concise terms all the collection, shipping and storage requirements for this program. In addition, the GD project coordinator will review the entire procedure with the appropriate collection centre/nursing staff members each time an appointment is booked for specimen collection. Confidentiality protocols will be stressed during all phases of the training procedure.

Collection: Specimens will be collected in (a) Gamma-Dynacare Ontario specimen collection centres, (b) Third party, Gamma-Dynacare contracted specimen collection centres and (c) home collections (mobile collection) by ComCare (a private nursing/home-visit corporation owned, in part, by GD).

All collections will use five (5) part chain-of-custody documentation. GD staff is already very familiar with this procedure from the drug testing programs currently in operation.

Two 7 mL SST tubes will be collected from each patient. SST tubes and all other specimen collection requirements including the chain-of-custody forms will be provided to the collection centre or to ComCare. Whole blood can be transported at 2-25°C but must be centrifuged and aliquoted within 6 hours of collection.

Aliquots of serum may be transported or stored at 2-8°C for up to 72 hours or stored indefinitely frozen at -70°C. In collection centres, drawn specimens will be allowed to clot for 20 minutes and then will be centrifuged at 1500 X g for twenty (20) minutes at room temperature. Aliquots (about 0.5 mL) will then be removed from the original tubes and placed into 1.5 mL polypropylene screw-cap tubes. These aliquot tubes will be placed into the freezer in the collection centre (refrigerators may be used if no freezer is available) and shipped to the GD Brampton laboratory that evening packed in dry ice.

The time and date of collection will be entered on the chain-of-custody requisition and will be transcribed by the data entry personnel into the GD laboratory information system and will appear on the laboratory report. The time and date of testing will be transcribed onto the laboratory report as well.

Shipping: Once blood is safely collected and properly identified, the specimen will be transported to the central laboratory (GDML) via IATA-approved shipping containers STP-100 and STP-300 with proper labeling and necessary supporting documentation.

An internal coordinator will be assigned to oversee the logistics of collection, storage and transportation of samples. This person will coordinate all laboratory aspects related to this proposal. This person will be assisted by a Clinical Microbiologist to provide specimen integrity and medical consultation if necessary. Presently, GD has trained staff in the proper handling of infectious materials.

The following team members will be available and fully informed of the testing requirements and logistics:

Julius Kapala, PhD, RSM (CCM)
Medical Microbiologist
Director of Microbiology
Gamma-Dynacare Medical Laboratories

Joel H. Goodman, PhD, FCACB
Clinical Chemistry
Vice-President, Clinical Operations
Gamma-Dynacare Medical Laboratories

Steve Brotherton, MSc
Clinical Trials Manager
Gamma-Dynacare Medical Laboratories
(Trained in IATA requirements and >8 years of clinical trial experience in Chronic Hepatitis C clinical trials)

Helen Pierson
Director of Patient Services
Gamma-Dynacare Medical Laboratories

Ann Cooper, RN
Business Development
Gamma-Dynacare Medical Laboratories

These personnel can be reached at 1-800-668-2714 Monday through Friday.

Collection Procedure: Patients will have 2 SST tubes drawn and labeled with a proper identifier following completion of a 5-part chain-of-custody form designed for this specific collection by GD.

The tubes will then be spun and aliquoted into 4 properly identified cryovial tubes (screw-top polypropylene aliquot tubes;1 for testing and 3 as backup) and placed in a Saf-T-Pak STP-100 and further placed on dry ice in a Saf-T-Pak Medifreez STP-300 container according to IATA requirements for storage and labeling. A tamper-proof seal will be placed on all cryovial containers to ensure specimen integrity. The specimen will be collected and transported to GD within 24 hours. Furthermore, a live person will be available by cell phone 24 hours a day as an Emergency Contact.

In the event that a GD courier picks up the specimen, transport of this specimen will be handled in compliance with the TDG Act and the Regulations thereof

Once the sample arrives at GD, trained, designated personnel will verify all documentation and sign off on the chain of custody form and store the individually-labeled sample in a secured -70° C freezer until testing.

Storage: Unused and unopened aliquots will be stored in proper chain-of-custody containers in -70°C freezers. These freezers are alarmed and have continuous temperature monitoring to provide a continuous record of the storage temperature. According to Roche's testing specifications, the aliquots can be frozen and thawed twice without a loss of any virus ("copy number"). It is anticipated that at least four aliquots from each patient will be stored in the freezers after the testing has been completed. All aliquots will be stored for a minimum of three years however no specimens will be discarded without the written permission of the administrator.

4. TESTING

All testing will be performed in GD's Brampton, Ontario facility. Specimens arrive in the laboratory in the IATA-approved infectious disease shipping containers in 1.5 mL polypropylene screw-cap aliquot tubes containing approximately 0.5 mL of serum each, frozen in dry ice. Within these shipping containers, the specimens are packaged in the chain-of-custody tamper-proof containers. "Dry-mat" to absorb any spilled material and an indicator of thawing is also contained in the shipping kit. Unpacked specimens and chain-of-custody requisitions are checked and the aliquots stored in the freezer at -70°C.

In preparation for testing, one aliquot is signed out and used for testing. The remaining aliquot tubes are returned to a chain of custody storage bag and stored at -70°C.

Testing is performed with the Roche Amplicor Hepatitis C Virus Test, v2.0. Three separate areas of the laboratory are used for (a) pre-amplification - reagent preparation area, (b) pre-amplification - specimen and control preparation area and (c) post-amplification – amplification and detection area. GD has been performing PCR-type testing routinely in the Brampton laboratory since early 1998.

A full quality control program will be implemented for this program and no specimens other than those for this program will be tested together. Unequivocal positive results will be recorded and reported to the administrator as "POSITIVE". Equivocal results will be repeated using a separate aliquot of plasma from the original aliquot tube. If unequivocally positive on this second test, result will be reported to the administrator as "POSITIVE". If still equivocal, test will be reported as "INDETERMINATE – SUGGEST REPEAT TEST". All unequivocally negative results will be repeated and confirmed as negative by both PCR as well as by EIA, prior to releasing a "NEGATIVE" result to the administrator.

Dr. Julius Kapala, our full-time microbiologist, will sign out all reports and is available to the program administrator or his/her designate at any time of day.

We suggest that in the event a patient disputes the negative result, they can (perhaps at their own expense?) ask the court to have a stored aliquot opened and re-tested. A second Canadian laboratory might be appropriate for this test (GD can suggest a non-GD affiliated laboratory that will be willing to perform the secondary testing).

All QC data will be stored and will be available to produce for the courts should this be requested. Contested results may require court testimony from the testing laboratory. GD will supply the medical expertise for court appearances, as required, at no additional charge to the administrator.

5. REPORTING

Hard copy of all results is the primary mode of reporting. These reports can be delivered to the program administrator via the GD courier system. Reports can be faxed as required, as well. Should an electronic reporting system be required, GD already reports electronically to many physician and clinical research offices. The GD format for data download will be provided to the administrator and we will assist in developing an electronic link if required.

6. COSTING

To simplify billing by GD to the system administrator, it is suggested that a single cost per patient pricing be employed. The pricing suggested is based on the assumption that collections will take place in the proportions outlined below.

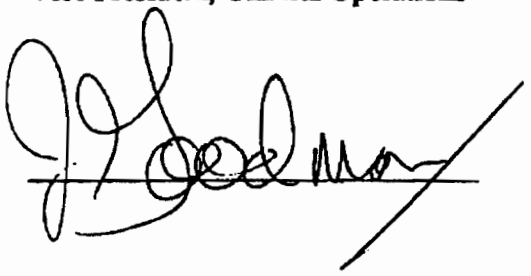
GD specimen collection centres	40%
Third party collection centres	50%
Home visits (ComCare)	10%

A complete outline of the proposed costs per patient are listed in Appendix One. Details of the costing are calculated at cost plus 20%. The figure of 20% was selected because of the uncertainty associated with the collection demographics as well as the number of repeat tests that will be required.

The cost for the testing will be an all-inclusive amount of $370.80 per patient. No other charges will be submitted.

Submitted by:

Dr. Joel Goodman, Ph.D., FCACB
Vice President, Clinical Operations



APPENDIX ONE

Collection Costs	49.20
Shipping Costs	61.20
Testing Costs	78.00
Material Costs	61.20
Reporting & Communication Costs	34.80
Storage	19.20
Administration	67.20
	$370.80

SUTTS, STROSBERG LLP
BARRISTERS & SOLICITORS

TELEPHONE
(519) 258-9333
(877) 316-4372(HEPC)
FAX
(519) 258-9503

E-MAIL
hep-c@strosbergco.com

MAILING ADDRESS
P.O. BOX 670
600-251 GOYEAU STREET
WINDSOR, ONTARIO, CANADA
N9A 6V4

HARVEY T. STROSBERG, Q.C.
E-mail: hts@strosbergco.com
Direct Dial (519) 561-6228
Direct Fax (519) 258-9503

OUR FILE NO. 44-800-000

April 17, 2000

VIA FACSIMILE

Post-it™ Fax Note 7671E	Date Apr 2000	# of pages ▸ 4
To Dr. Joel Goodman	From Pat Speight	
Co./Dept.	Co.	
Phone # 905 790 3000	Phone # 519 258 9333	
Fax # 905 790 2990	Fax # 519 258 9527	

Dynacare Laboratories
115 Midair Court
Brampton ON L6T 5M3

Fax: (905) 790-3412
Tel: (905) 790-3000

 # PAGES: 4 **TIME SENT:** 2.22 AM (PM)

Gentlemen/Mesdames:

The Hepatitis C 1986-1990 Class Action Settlement: Request for Proposals

REQUEST FOR PROPOSALS

This letter is a Request for Proposal to provide Hepatitis C virus - Polymerase Chain Reaction HCV ("PCR") testing and services.

BACKGROUND

The courts of British Columbia, Ontario and Quebec (the "Courts") have approved a settlement agreement for persons who were infected with the Hepatitis C virus ("HCV") for the first time by a blood transfusion in Canada in the period January 1, 1986 to July 1, 1990 (the "Class Period"), for hemophiliacs and persons with thalassemia major who received blood or blood products in the Class Period and are infected with HCV; and for secondarily infected spouses, partners and children.

The settlement agreement provides that a certain lump sum will be paid to persons who were infected with HCV by blood

in the Class Period and who deliver a positive HCV-PCR test which demonstrates the presence of the virus in the blood of the person. The theory is that the PCR test is proof of ongoing infection with HCV.

TESTING WILL BE REQUISITIONED BY THE ADMINISTRATOR

The HCV-PCR testing is not for "diagnosis, prophylaxis or treatment" and will be requisitioned by the Administrator of the settlement agreement for purposes of assessing compensation.

YOUR PROPOSAL WILL BE REVIEWED BY THE COURTS

The proposals for HCV-PCR testing and services will be reviewed by the Courts. Acceptance of a proposal will be by order of the Courts.

PROPOSED COLLECTION LOGISTICS FOR PATIENTS REQUIRING PCR TESTING

The estimated number of persons expected to come forward for the HCV-PCR test will be approximately 1000 to 5000. They are located across Canada. The testing may go on for many years, but the proposal should encompass a time frame of at least three years. The proposal should also clearly set out how the blood collection will be performed across Canada.

METHOD OF COLLECTION AND STORAGE

Blood collected for HCV-PCR testing must be collected in special, sterile collection tubes (SST, EDTA) in the amount of 14 ml. Please specify the methods to be utilized and the timing for the collection, transportation, storage (including the types of containers) and centrifuging of the samples and the temperature at which each step will be performed.

If a preferable method of collection and storage becomes available during the currency of the contract then that preferable method shall be used.

PERSONNEL

All personnel involved with specimen collection, handling, aliquoting, storage or shipping must be trained in the specific requirements for this testing. During the training process, great care must be taken to ensure that all staff recognize the sensitivity of the issues and the absolute necessity for flawless documentation.

SHIPPING

The proposal must specify how specimens will be shipped. All shipping containers must comply with all current IATA and provincial regulations.

LOCATION OF TESTING AND HANDLING

The proposal must specify where the testing will be performed. The location(s) must have familiarity with PCR-type technology, and that technology must be in routine use at the laboratory. A medical microbiologist (MD or PhD) must sign out each report and provide medical consultation whenever necessary. Documented chain-of-custody will be required for each specimen.

If a preferable method of testing becomes available during the currency of the contract then that preferable method shall be used.

The proposal should explain how testing will be done and how quality control will be maintained. The data may be required for court hearings.

The proposal must set out the procedure for storing the aliquots of serum not used for testing. We suggest storage at -70°C for 3 years.

REPORTING

The proposal should provide particulars of how results will be communicated to the Administrator which must include the ability to report results electronically. Reporting of results must maintain patient confidentiality. The reporting of results must include the date and time of collection and the date and time of testing.

LANGUAGE REQUIREMENTS

The proposal must include confirmation that with respect to specimen collection you can provide service in both official languages on demand.

COSTING

The proposal must include detailed costing. The lowest or any particular proposal will not necessarily be accepted.

RESPONSE TO REQUEST FOR PROPOSALS

For further information about this Request for Proposals, please contact Harvey T. Strosberg at telephone number (519) 561-6228, fax number (519) 258-9503.

A written response to this request for proposal should be sent to:

Harvey T. Strosberg
Sutts, Strosberg LLP
Barristers and Solicitors
600-251 Goyeau Street
Windsor ON N9A 6V4

Proposals will be accepted up to 5:00 p.m. on April 28, 2000.

This Request for Proposals may or may not result in the award of a contract.

Yours very truly,

Harvey T. Strosberg

Harvey T. Strosberg

HTS/ba

G:\LIT\CLASS\Hspc\Letters\proposals-040600.doc

DIANNE LOUISE PARSONS et al.
JAMES KREPPNER et al.
Plaintiffs

THE CANADIAN RED CROSS SOCIETY et al.
Defendants

Court File No. 98-CV-141369 c.p
98-CV-146405 c.p

ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDINGS COMMENCED AT TORONTO

ORDER

SUTTS, STROSBERG LLP
Barristers and Solicitors
600 Westcourt Place
251 Goyeau Street
Windsor ON N9A 6V4

HARVEY T. STROSBERG, Q.C.
Tel: (519) 258-9333
Fax: (519) 258-9527

FILE: 44-900-000
REF: HTS/sw

THE ATTACHED IS EXHIBIT "D" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Court File No. 98-CV-141369 cp

ONTARIO
SUPERIOR COURT OF JUSTICE

THE HONOURABLE MR. JUSTICE	)	THURSDAY, THE 10TH DAY
	)	
WARREN K. WINKLER	)	OF MAY, 2000

BETWEEN:

DIANNA LOUISE PARSONS, MICHAEL HERBERT CRUICKSHANKS, DAVID TULL, MARTIN HENRY GRIFFEN, ANNA KARDISH, ELSIE KOTYK, Executrix of the Estate of Harry Kotyk, deceased and ELSIE KOTYK, personally

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO and THE ATTORNEY GENERAL OF CANADA

Defendants

Proceeding under the *Class Proceedings Act, 1992*

Court File No. 98-CV-146405 cp

BETWEEN:

JAMES KREPPNER, BARRY ISAAC, NORMAN LANDRY, as Executor of the Estate of the late SERGE LANDRY, PETER FELSING, DONALD MILLIGAN, ALLAN GRUHLKE, JIM LOVE and PAULINE FOURNIER as Executrix of the Estate of the late PIERRE FOURNIER

Plaintiffs

and

THE CANADIAN RED CROSS SOCIETY, THE ATTORNEY GENERAL OF CANADA and HER MAJESTY THE QUEEN IN RIGHT OF ONTARIO

Defendants

Proceeding under the *Class Proceedings Act, 1992*

ORDER

THIS MOTION, made by the representative plaintiffs, was heard this day at Toronto, Ontario.

THIS COURT HAVING ORDERED a *de novo* consideration of the appointment of an Administrator on December 24, 1999 and that Madame Justice Morneau of the Superior Court of Quebec, Mr. Justice Smith of the Supreme Court of British Columbia and this court confer for the purposes of deciding upon the appointment of the Administrator;

AND ON HAVING REVIEWED the transcripts of proceedings and exhibits entered into evidence before Madame Justice Morneau on January 27 and 28, 2000 and February 17 and 18, 2000 in *Honhon et al* v. *Canada et al.* Action No.500-06-000016-200;

AND ON HAVING CONFERRED with Madame Justice Morneau and Mr. Justice Smith for the purpose of deciding the appointment of an Administrator;

AND ON READING the affidavits of Patricia A. Speight, sworn April 7, 2000, Mark Rambin, sworn May 8, 2000 and David Robins, sworn May 9, 2000;

AND ON HEARING the submissions of counsel for the representative plaintiffs and counsel for Crawford Adjusters Canada Incorporated/Expertises Crawford Canada Incorporée and Garden City Group Inc. ("Crawford");

AND ON BEING ADVISED of the consent of Crawford to the terms of Schedule "A" to this order ("Amended Schedule 3");

1. THIS COURT ORDERS AND DECLARES that since the Ontario Class Actions have been stayed against the CRCS by the order of Mr. Justice Blair made on July 20, 1998 in action no. 98-CL-002970 (Toronto) (the "Stay"), the Stay having been subsequently extended by further orders of the Court made on August 19, 1998, October 5, 1998, January 18, 1999, May 5, 1999, July 28, 1999 and February 25, 2000, nothing in this order is to have the effect of prejudicing the CRCS.

2. THIS COURT ORDERS that the definitions set out in paragraph 2 of the judgment issued on the 22nd day of October, 1999 (the "October 22, 1999 judgment") apply to this order.

3. THIS COURT ORDERS that the October22, 1999 judgment be and is hereby amended:

(a) by striking out of paragraph 14 the words "Peterson Worldwide LLC, a limited liability company incorporated under the laws of the State of Illinois and Reed Consulting, Ltd., an Ontario corporation, carrying on business as Peterson Worldwide LLC of Canada" and substituting the words "Crawford Adjusters Canada Incorporated/Expertises Crawford Canada Incorporée and Garden City Group Inc." so that paragraph 14 reads as follows:

> 14. THIS COURT ORDERS that Crawford Adjusters Canada Incorporated/Expertises Crawford Canada Incorporée and Garden City Group Inc. be and are hereby appointed, with joint and several liability, as the Administrator of the Plans until further order of the Courts on the terms and conditions and with the powers, rights, duties and responsibilities set out in Schedule 3.

and,

(b) by striking out Schedule 3 and substituting Amended Schedule 3 in its place.

4. THIS COURT ORDERS that Royal Trust shall pay $2,468,437 to Peterson Worldwide LLC, a limited liability company incorporated under the laws of the State of Illinois and Reed Consulting Ltd., an Ontario corporation carrying on business as Peterson Worldwide LLC of Canada, in full and final satisfaction of all claims that they have for services rendered and expenses incurred directly or indirectly to or for the benefit of the Plans, Class Action Counsel, the Joint Committee, Fund Counsel, the FPT Governments, the Class Members and for all claims of any nature and kind which they have or may have, directly or indirectly, relating to the administration of the Plans, to the Class Members, to the operation of the Claims Centre (as defined in Schedule 3 of the October 22, 1999 judgment), and for their dealings with Class Action Counsel, the Joint Committee, Fund Counsel and the Class Members.

5. THIS COURT DECLARES that Peterson Worldwide LLC of Canada and Reed Consulting Ltd., an Ontario corporation carrying on business as Peterson Worldwide LLC of Canada ("Releasors") have released, subject to the indemnity contained in Schedule 3 of the October 22, 1999 judgment, the Plans, Class Action Counsel, the Joint Committee,

Fund Counsel, the FPT Governments and the Class Members from any and all actions, liabilities, claims, debts and demands of every nature and kind for quantum meruit, damages, indemnity, costs, expenses and interest which the Releasors ever had, now have or may hereafter have in any way relating to or arising from the administration of the Plans, the operation of the Claims Centre and their dealings with the Plans, the Agreement, Class Action Counsel, the Joint Committee, Fund Counsel, and the Class Members.

6. THIS COURT ORDERS that Crawford be and are hereby appointed as of March 9, 2000, with joint and several liability, as the Administrator of the Plans until further order of the Courts on the terms and conditions and with the powers, rights, duties and responsibilities set out in Amended Schedule 3.

7. THIS COURT ORDERS that the April 1, 2000 to March 31, 2001 budget for Crawford, attached as Schedule "B" to this order, be and the same is hereby approved.

8. THIS COURT ORDERS that Royal Trust Company shall pay to Crawford $305,072.02 for services rendered to March 31, 2000.

9. THIS COURT ORDERS that Royal Trust Company shall pay Crawford $405,828.46 (inclusive of G.S.T.) per month as their monthly budget payment from and after April 1, 2000 for the term of their appointment or until further order of the Courts.

10. THIS COURT ORDERS that Crawford shall at least annually present their accounts for services rendered to the Courts and account for the monthly budget payments received by them.

11. THIS COURT DECLARES that the payments particularized in this order shall not be made by Royal Trust Company until they are also authorized by the courts of British Columbia and Quebec.

12. THIS COURT ORDERS that this order shall be issued, entered and then filed in the Ontario Transfused Class Action Court file numbered 98-CV-141369 and the Ontario Hemophiliac Class Action Court file numbered 98-CV-146405.

JUSTICE

ENTERED AT/INSCRIT À TORONTO
ON/BOOK NO.
LE/DANS LE REGISTRE NO.:
JUN 22 2000
AS DOCUMENT NO.:
À TITRE DE DOCUMENT NO.:
PER/PAR:

SCHEDULE "A"

SCHEDULE 3

TERMS OF APPOINTMENT OF ADMINISTRATOR

INTERPRETATION

1. (1) In this Schedule, the following terms shall have the meanings set out below:

(a) **Administrator**: means the administrator appointed by the Courts from time to time to administer the Plans;

(b) **Annual Budget**: has the meaning given in section 25 of this Schedule;

(c) **Approval Orders**: means the judgements or orders of the Courts to be granted approving the Agreement as being a good faith, fair, reasonable and adequate settlement of the Class Actions pursuant to the class proceedings legislation in British Columbia, Ontario and Quebec;

(d) **Assets**: has the meaning given in section 11 of this Schedule;

(e) **Auditors**: means the auditors appointed by the Courts and their successors appointed from time to time pursuant to the provisions of Articles Eight and Ten of the Agreement;

(f) **CAC**: means Crawford Adjusters Canada Incorporated/Expertises Crawford Canada Incorporée;

(g) **Claims Centre**: has the meaning given in subsection 9(g) of this Schedule;

(h) **Crawford**: means CAC and GCG;

(i) **Force Majeure Event**: has the meaning given in section 30 of this Schedule;

(j) **Funding Agreement**: means the funding agreement made as of June 15, 1999 which is annexed as Schedule 2 to the Judgment of the Ontario Superior Court of Justice on October 22, 1999;

(k) **GCG**: means The Garden City Group Inc.;

(l) **including**: means including without limitation, and "include" and "includes" have a corresponding meaning;

(m) **Initial Term Confirmation Date**: means, for the purpose of this Schedule only, March 9, 2000;

(n) **Joint Committee**: means, a committee of four persons comprised of one Class Action Counsel from each of the Transfused Class Actions and one Class Action Counsel from the Hemophiliac Class Actions;

(o) **Lease**: has the meaning given in subsection 43(1) of this Schedule;

(p) **Monthly Report**: has the meaning given in section 20 of this Schedule;

(q) **Premises**: has the meaning given in subsection 43(1) of this Schedule;

(r) **Quarterly Budget**: has the meaning given in section 25 of this Schedule;

(s) **Quarterly Report**: has the meaning given in section 22 of this Schedule;

(t) **Service Performance Criteria**: has the meaning given in section 9 of this Schedule; and

(u) **Trustee**: means the trustee appointed by the Courts and its successors appointed from time to time pursuant to the provisions of Articles Six and Ten.

(2) Capitalized terms used but not defined in this Schedule shall have the meaning given to such terms in the Approval Orders.

APPOINTMENT AS ADMINISTRATOR

2. Crawford shall administer the Plans in accordance with the provisions of the Agreement, the Plans, the Approval Orders and all administration protocols approved by the Courts and any directions provided by the Courts. Crawford acknowledges and agrees that it does not have any right, title or interest in the Trust Fund. Notwithstanding anything herein to the contrary, the payment of approved claims by Crawford shall at all times be deemed to have been made from the Trust Fund and all funds required for such purpose shall remain subject to the trust settled and established pursuant to the Funding Agreement until such time as such payment shall have been made.

REPRESENTATIONS, WARRANTIES AND COVENANTS

3. Crawford shall be deemed to have represented, warranted and covenanted to the Courts and to the Trustee for the benefit of the Trust as of the date hereof as follows (and such representations, warranties and covenants shall be deemed to survive for a period ending on the day immediately following the sixth anniversary of the date on which Crawford ceases to be the Administrator):

(a) GCG is a corporation duly incorporated and organized, validly existing and in good standing under the laws of the State of Delaware, United States of America;

(b) CAC is a corporation duly incorporated and organized, validly existing and in good standing under the laws of Canada;

(c) GCG and CAC are wholly-owned subsidiaries of Crawford & Company, a corporation duly incorporated and organized, validly existing and in good standing under the laws of the State of Georgia, United States of America;

(d) Crawford has all necessary power, authority and capacity to consent to the Approval Orders and all agreements and instruments to be executed by it as

contemplated by the Approval Orders and to carry out its obligations under the Approval Orders and under such agreements and instruments. The consent by Crawford to the Approval Orders and the execution and delivery by Crawford of any such agreements and instruments and the performance by Crawford of its obligations contemplated hereby and thereby have been duly authorized by all necessary corporate action on the part of Crawford;

(e) Crawford irrevocably and unconditionally attorns and submits to the jurisdiction of the Courts, will not oppose any action or proceeding on the basis of *forum non conveniens* or for any other jurisdictional grounds and will not oppose the enforcement against it in any other jurisdiction of any final judgment or order duly obtained from the Courts, and irrevocably appoints the following person as its agent to receive on its behalf service of summons and any other legal process which may be served in any action, suit or proceeding: Mr. Howard M. Drabinsky, Lang Michener, BCE Place, Suite 2500, 181 Bay Street, Toronto, Ontario, M5J 2T7;

(f) Each of the Approval Orders and any agreements and instruments to be executed by Crawford as contemplated by the Approval Orders constitutes a valid and binding obligation of Crawford, enforceable against Crawford in accordance with their respective terms subject, however, to limitations on enforcement imposed by bankruptcy, insolvency, reorganization or other laws affecting the enforcement of the rights of creditors or others and to the extent that equitable remedies such as specific performance and injunctions are only available in the discretion from the Courts in which they are sought;

(g) The consent by Crawford to the Approval Orders and the execution and delivery by Crawford of any agreements and instruments contemplated hereby, and the performance of Crawford's obligations hereunder and thereunder, (i) have been duly authorized by all requisite actions on the part of Crawford, (ii) will not violate (A) any provision of any applicable law or of the constating documents or by-laws of Crawford, (B) any order of any government, court or other governmental body or (C) any provision of any indenture, agreement or other instrument to which Crawford is a party or by which it or any of its property is bound or (iii) be in conflict with, result in a breach of or constitute (alone or with notice or lapse of time or both) a default under any such indenture, agreement or other instrument, and no action, consent or approval of, registration or filing with or any other action by any other government, court or other governmental body is or will be required on the part of Crawford in connection with the Approval Orders or any agreements or instruments contemplated hereby, except for such as has been made and is in effect;

(h) There are no actions, suits or proceedings at law or in equity or by or before any government, court or other governmental body now pending or, to Crawford's knowledge, threatened against or affecting Crawford, which would have a material adverse effect on Crawford's ability to perform its duties as Administrator;

(i) The individuals consenting to the Approval Orders on behalf of Crawford have the capacity to do so;

(j) Crawford is currently not in a position of conflict of interest with respect to the administration of the Plans and Crawford shall promptly notify the Joint Committee if such a conflict does arise;

(k) Crawford's conduct of the administration of the Plans has not infringed, and will not infringe, upon the industrial or intellectual property rights of any third party;

(l) GCG is the owner and CAC is the licensee, free and clear of all liens and rights of third parties of certain computer programs and related materials known as the HCV Claims Processing System (the "**CLASS Software**") to be used in the administration of the Plans;

(m) Crawford has sufficient resources, experience and expertise to perform its duties as Administrator, and will utilize the same to perform such duties on a commercially reasonable and prudent basis; and

(n) None of the agreements entered, or to be entered, into by Crawford for the provision of goods or services in respect of Crawford's administration of the Plans contains, or will contain, any commercially unreasonable or imprudent assignment or termination provision.

INITIAL TERM, RENEWALS AND TERMINATION

4. Subject to further order of the Courts, the initial term of this appointment is for a period of five years from March 9, 2000.

5. Any renewal of the appointment of Crawford as Administrator for any period or periods subsequent to the initial five year term will be in the Courts' discretion. The Joint Committee will provide Crawford at least 210 days written notice of its decision as to whether or not it will seek to renew the appointment of Crawford as Administrator.

6. The Joint Committee may, at any time upon 15 days written notice to Crawford, bring a motion for an order terminating the appointment of Crawford as Administrator for cause. Cause shall consist of any one of the following:

(a) The material or repeated failure of Crawford to meet the Service Performance Criteria, but only after Crawford having received a written notice from the Joint Committee with respect to any such failure or pending failure, and Crawford not curing such failure within a period of 30 days following its receipt of such notice (provided however that notice under this subsection 6(a) shall not be required in respect of a breach of section 15 of this Schedule);

(b) Where:

(i) Crawford fails to contest, by appropriate proceedings promptly initiated and diligently conducted, an involuntary bankruptcy, insolvency, or re-

organization proceeding or a proceeding for an arrangement or composition with creditors filed against Crawford, or fails to vacate the same within 60 days after the date of such filing;

(ii) Crawford, or any of its affiliates (within the meaning of the *Canada Business Corporations Act*) or shareholders initiates any proceeding referred to in clause (i) or makes an assignment for the benefit of its creditors or takes advantage of any statute providing for the relief of debtors;

(iii) Crawford fails to contest, by appropriate proceedings promptly initiated and diligently conducted, the appointment of a receiver, receiver and manager, or trustee for Crawford or for any of its assets, or fails to vacate the same within 60 days after such appointment;

(iv) Crawford ceases to do business as a going concern or ceases to conduct its operations in the normal course of business; or

(v) Crawford directly or indirectly and whether through a sale, reorganization, distribution or otherwise, disposes of, or there is seized by any creditor of Crawford, all or any material part of its business or assets forming part of or used in its operations as Administrator (provided that Crawford shall be permitted to transfer all or any part of such business or assets to a wholly-owned affiliate of Crawford & Company that is incorporated in Canada or the United States of America (but, for greater certainty, will continue to be obliged to administer the Plans from the Claims Center in Ottawa, Canada) and, in such event, Crawford shall be jointly and severally liable with such affiliate of Crawford & Company with respect to its obligations as Administrator); provided that the acquisition of Crawford & Company shall not constitute an indirect sale, acquisition or other disposal of Crawford. Crawford will notify the Joint Committee of any such acquisition;

(vi) Any other action or inaction on the part of, or within the control of, Crawford or any of its affiliates (within the meaning of the *Canada Business Corporations Act* or other circumstances or events affecting Crawford which may bring the administration of the Plans into disrepute with a material proportion of the Class Members or of the public or which may materially adversely affect the sufficiency of the Trust Fund;

(c) Wilful misconduct on the part of Crawford; and

(d) Where Crawford fails to comply with section 8 of this Schedule but only after Crawford having received a written notice from the Joint Committee with respect to such failure has failed to cure such default within a period of 30 days following receipt of such notice.

7. Upon its removal as Administrator, or upon termination of its appointment as Administrator:

(a) Crawford shall promptly:

(i) Deliver to the Trustee or a new Administrator approved by the Courts (as directed by the Joint Committee) at no charge (save reimbursement for reasonable out-of-pocket costs of delivery) all Claimants' Data in all such media and formats as then maintained by Crawford (including then-current machine-readable form); provided that if the Trustee or new Administrator requests that any Claimants' Data be delivered in a specific media or format other than that used by Crawford, then Crawford shall provide such Claimants' Data in such media and format and, for doing so, Crawford shall be entitled to compensation at and on its then-current applicable rates. Crawford shall not retain any copies of any Claimants' Data;

(ii) To the extent assignable, assign and convey to the Trustee or a new Administrator approved by the Courts (as directed by the Joint Committee), all of Crawford's rights and interests in any and all of such of the contracts and licenses entered into or obtained in respect of the administration of the Plans as the Joint Committee directs, including in respect of any websites, e-mail addresses, telephone and facsimile numbers and leases of premises for an aggregate consideration of $1.00;

(iii) Grant to the Trustee or a new Administrator approved by the Courts (as directed by the Joint Committee), a perpetual, irrevocable, exclusive, royalty-free transferable right, in Canada, the United States of America and in any other jurisdiction necessary to permit the administration of the Plans, to copy, modify, develop, sub-license and otherwise use the addresses, telephone and facsimile numbers, e-mail addresses, websites, domain names and logos which relate to the administration of the Plans, to the extent such grant is permissible at law;

(iv) At the Joint Committee's option, exercisable in respect of all or any part of the following:

(A) grant to the Trustee or a new Administrator approved by the Courts (as directed by the Joint Committee) a perpetual, worldwide, irrevocable, non-exclusive, transferable right to execute, copy, modify, develop, sub-license and otherwise use only for the administration of the Plans (subject to a $3,000 Canadian monthly software licence fee): the CLASS software and database (including any enhancements of same) until such time as the Joint Committee or subsequent Administrators cease using, in the Joint Committee's unfettered discretion, the CLASS software and return such software to Crawford (at which time the above-referenced licence fee shall no longer be payable); and any other software, software modifications, calculation templates, databases or other intellectual property or modifications thereof developed by or for Crawford for use in the administration of the

Plans (other than off-the-shelf commercially available software); and

(B) provide to the Trustee or a new Administrator approved by the Courts the version of the CLASS software and database being used at the time of termination, including, without limitation: upgrades, enhancements, new releases, patches and updates to the CLASS Software made up to and including the time of termination.

provided that all of the foregoing, including the CLASS software, shall be licensed or delivered (as applicable) on an "as is" basis and without any warranties concerning the operation, functionality or suitability of same; and

(C) To the extent permissible at law, assign and convey to the Trustee or a new Administrator approved by the Courts (as directed by the Joint Committee) any or all of the other Assets not addressed in subsections (i) to (iv) as the Joint Committee may direct, free and clear of all liens and other encumbrances, other than liens or encumbrances associated with the leasing of assets, for an amount equal to the greater of (x) that portion purchase price of the Assets that has not been reimbursed by the Trust Fund, if any, and (y) $1.00 in the aggregate.

provided that all the foregoing assets shall be transferred or assigned by Crawford on an "as is" basis and without any warranties concerning the operation, functionality or suitability of same;

(b) The Joint Committee or a new Administrator approved by the Courts shall be entitled, without any liability to Crawford, to offer employment to Canadian personnel engaged by Crawford in connection with the administration of the Plans; and

(c) Crawford shall provide such termination assistance services (other than those provided for in subsection (a)) as may reasonably be requested by the Joint Committee and, in connection therewith, shall be entitled to compensation at and on its then-current generally applicable rates and other terms.

Upon the acceptance of the assignment or transfer of any of the Assets set forth in this Section 7, the Joint Committee or a new Administrator appointed by the Courts shall assume all future obligations and liabilities with respect to such Assets and Crawford shall be indemnified and held harmless by the Trust Fund from all claims, costs and reasonable fees arising out of the Joint Committee's or new courts-appointed Administrator's use of such Assets.

7A. Except as otherwise provided in this Schedule 3, it shall be a condition of the rights to be granted in section 7(a)(iv)(A) that the Trustee or the new Administrator, as the case may be, (the "**licensee**") acknowledge that:

(a) GCG is the sole owner of all proprietary rights relating to the CLASS Software and that the CLASS Software is exclusively the property of GCG;

(b) the CLASS Software may not be copied in whole or in part except for archival purposes;

(c) the licensee may not, for any purpose or under any circumstances, use the CLASS Software to provide data processing or claims administration services to any third party other than in connection with the Project, and the licensee shall not sell, assign (other than, upon the licensee's removal as Administrator, to the Trustee or a new Administrator approved by the courts), rent, or reproduce the CLASS Software, or develop derivative products, or use the CLASS Software for any purpose other than the Project; and

(d) on-going maintenance for the CLASS Software and upgrades, enhancements, new releases, patches and updates to the CLASS Software made after the time of termination of Crawford as Administrator shall be made available to the Trustee or a new Administrator at commercial rates to be agreed by the parties or set by the Courts.

SOFTWARE ESCROW

8. Within 120 days of the Initial Term Confirmation Date, Crawford shall place the source code(s) for the CLASS software and CLASS database, and of any other software, modifications or calculation templates, databases or other intellectual property or modifications thereof, in escrow in favour of the Trustee or a new Administrator approved by the Courts, pursuant to an agreement on commercially reasonable terms and conditions to be approved by the Joint Committee and Fund Counsel. Such agreement shall provide that the escrow agent shall maintain such materials in escrow and provide them to the Trustee or new Administrator approved by the Courts if so directed by the Joint Committee or the Courts.

SERVICE PERFORMANCE CRITERIA

9. Crawford shall achieve the Service Performance Criteria. The **Service Performance Criteria** are that, at all times on and after 180 days following the Initial Term Confirmation Date, Crawford shall, in all material aspects, be in compliance with the following service levels and other conditions and with sections 10 to 15, both inclusive, of this Schedule:

(a) Crawford shall have established, tested, made operational and demonstrated to the Joint Committee, if requested, substantially all of the necessary computer system and all other resources required to administer the Plans in all respects (including accurately capturing all data deemed relevant to the Administrator to a calculation defined in the Agreement, computing the terms of the Agreement applicable to each Class Member, maintaining all information required for reporting purposes, maintaining historical information received in respect of each Class Member and documenting the processes and calculations undertaken by the computer system);

(b) Crawford shall have substantially developed all forms and procedures required therefor (with the approval of the Joint Committee where required).

(c) Crawford shall maintain a bilingual toll-free telephone service to be operated by live operators at times to be designated by Crawford and approved by the Joint Committee to accommodate access by Class Action Members in all provinces and territories of Canada, supplemented by an interactive voice response system proposed by Crawford and approved by the Joint Committee;

(d) Crawford shall dedicate personnel, equipment and computer hardware and software resources, including individuals of suitable training and skill and with fluent English, French and bilingual (English and French) capabilities as appropriate to conduct the administration of the Plans.

(e) Crawford shall ensure that the most senior permanent staff person of the Claims Centre is able to read, write and speak both English and French proficiently;

(f) Crawford shall dedicate personnel specifically to assist Class Members or Claimants with their inquiries with respect to the claims application and appeal processes;

(g) Crawford shall operate a dedicated claims centre in Ottawa, staffed with sufficient personnel to meet the requirements set out herein (the "**Claims Centre**");

(h) Crawford shall maintain the personnel, hardware and software and other resources necessary for a computerized claims processing centre to function in a commercially reasonable manner;

(i) Crawford shall respond to all inquiries (oral or written) from Class Members, the Trustee, the Auditors, Fund Counsel, Claimants and the Joint Committee within 30 days of such inquiry;

(j) Unless exceptional circumstances dictate otherwise, Crawford shall make a decision on a claim and advise the claimant of the decision no later than 30 days after the receipt of all relevant information;

(k) Crawford shall, subject to Crawford receiving funds from the Trustees and unless exceptional circumstances dictate otherwise, make the approved payment to all Class Members within 45 days of the payment being approved;

(l) Crawford shall use its best efforts to ensure that its personnel provide timely, helpful and supportive assistance to Class Members and persons seeking to determine whether they are Class Members in completing the claims application process and in responding to inquiries;

(m) Crawford shall not make any payment to any claimant who, to Crawford's knowledge at the time of payment, did not meet the requirements for payment pursuant to the Agreement, the Plans, the Approval Orders and the administration protocols approved by the Courts; and

(n) Crawford shall make all payments to claimants in accordance with administration protocols approved from time to time by the Courts.

10. Crawford shall perform all services in a commercially reasonable and prudent manner and in accordance with the standards to be expected of a claims administrator.

11. Crawford shall, at all times while subject to the Approval Orders, maintain all the assets located at the Claims Centre that do or will form a part of or be used in Crawford's operations as Administrator (collectively, the "**Assets**") free and clear of any liens and other encumbrances, other than liens and other encumbrances associated with the leasing of assets.

12. Crawford shall, at all times while subject to this Order, maintain the following types of insurance with reputable carriers and for such risks, in the following amounts and having such other terms as an experienced prudent person administering the Plans would determine:

(i) general liability insurance with an aggregate limit of $2,000,000;

(ii) worker's compensation insurance with an aggregate limit of $1,000,000; and

(iii) professional liability insurance, including coverage for errors and omissions, with an aggregate limit of $10,000,000.

If the Joint Committee so directs, the Trustee shall be identified as a named co-insured on such insurance as the Joint Committee directs. The Joint Committee may direct Crawford to obtain and maintain such further insurance in respect of the administration of the Plans as the Joint Committee deems advisable and the costs thereof shall be paid by the Trust Fund.

13. Crawford shall establish and maintain a commercially reasonable and prudent business recovery plan. In the event of a disaster and as part of the business recovery plan, Crawford shall use its best efforts to restore the provision of services for the administration of the Plans in accordance with such plan and any direction from the Joint Committee as to the priority for re-establishment of services.

14. Subject to a prior termination of Crawford pursuant to section 6 of this Schedule or otherwise, in the event of any material or repeated failure of Crawford to meet the Service Performance Criteria or any of its other obligations contemplated by the Approval Orders, Crawford shall promptly perform a root-cause analysis to identify the cause of such failure and provide a report to the Joint Committee detailing the cause of such failure, a procedure for correcting such failure and a corrective action plan to address any possibility of the re-occurrence of such failure. The procedure and plan must be mutually acceptable to both Crawford and the Joint Committee. If the results of the root cause analysis demonstrate that such failure was substantially attributable to Crawford, then Crawford shall bear the cost of performing such analysis.

15. Crawford shall not accept from or provide to any person any improper commission, payment or other form of benefit in connection with the administration of the Plans or otherwise fail to honestly administer the Plans.

CERTAIN THIRD PARTY MATTERS

16. Crawford's obligation to achieve the Service Performance Criteria within the respective time periods specified below shall be subject to the timely performance by third parties, including the Joint Committee, of their respective duties contemplated in the Approval Orders which are necessary to enable the Administrator to achieve such criteria, including the approval of administration protocols, and such time periods shall be extended commensurate with any delays by any such third parties in the performance of such duties.

17. The Joint Committee will, on a timely basis, establish appropriate priorities for itself and for the provision of administrative services by Crawford, and communicate same to Crawford.

18. If, in Crawford's opinion, Crawford is not able to carry out, or is delayed in carrying out, the Service Performance Criteria, including where such inability or delay is attributable to third parties, then Crawford shall promptly provide the Joint Committee with notice of such inability or delay.

REPORTING AND ACCOUNTABILITY

19. Subject to any confidentiality restrictions imposed by law, Crawford shall provide the Auditor with reasonable access (including on-line access) during normal business hours to all facilities used by Crawford in the administration of the Plans, including access to computer hardware and software maintained at the Claims Centre used for such purposes; provided, however, that Crawford shall not be obligated to provide the Auditor with access to the source code for the CLASS Software unless, in the reasonable opinion of the Auditor, such access is necessary to permit the Auditor to carry out its duties and responsibilities.

20. Crawford shall prepare a report of its activities on a monthly basis in a form approved by the Joint Committee (the "**Monthly Report**").

21. The Monthly Report shall be forwarded to the Joint Committee 15 days following each month to which the report relates.

22. Crawford shall, on a quarterly basis, prepare a report of its activities in a form approved by the Joint Committee (the "**Quarterly Report**").

23. Crawford shall provide the Quarterly Report to the Joint Committee and Fund Counsel 30 days following each quarter year to which the report relates.

24. Crawford shall, within 15 days, or such greater time as may be reasonable in the circumstances, respond in reasonable detail to any inquiries or concerns expressed to it in writing by the Joint Committee or Fund Counsel, including an explanation as to the relevant circumstances and any proposal to remedy any problems.

BUDGETS, FEES AND EXPENSES

25. As soon as possible following the appointment of Crawford as administrator and at least 30 days prior to the beginning of each year and each quarter thereafter, Crawford shall provide to the Joint Committee a budget, respectively, for the following year (broken down by month) (the

"**Annual Budget**") and the following quarter (broken down by month) (the "**Quarterly Budget**"), as applicable. The Annual Budget and the Quarterly Budget shall include the following:

(a) Estimated fees and reimburseable expenses to be charged to the Trust Fund broken down to show categories of fees and reimbursable expenses in a format reasonably acceptable to the Joint Committee;

(b) Estimated staffing levels;

(c) Estimated volume of calls and other communications with the Claims Centre;

(d) Estimated volumes of claims to be processed; and

(e) The actual numbers in respect of items a. through d. above for the preceding year or quarter, as applicable; and

(f) Other assumptions on which the budget is based.

26. The Annual Budget shall require the approval of the Joint Committee and the Courts. The Quarterly Budget shall require the approval of the Joint Committee.

27. (1) For serving as the Administrator, Crawford shall be entitled to receive as an administration fee and for its reimbursable expenses, on a monthly basis, an amount calculated in accordance with the applicable Annual Budget. Payment of such administration fees and reimbursable expenses will be due 30 days after the Joint Committee receives the invoice relating thereto.

(2) The parties acknowledge the budget estimates contained in Crawford's proposal to the Joint Committee attached as Appendix A shall serve as the initial baseline for the Annual Budgets, and shall be adjusted as necessary to reflect the differences between the assumptions upon which the budget estimates were based and the actual or anticipated assumptions for the Annual Budgets as the administration of the Plans is performed.

28. (1) Crawford shall not be paid or reimbursed for any amount in excess of 115% of the estimated fees or reimbursable expenses set out in the Annual Budget unless, prior to the incurring of the relevant fees or expenses, Crawford receives the written consent of the Joint Committee.

(2) In the event that any proposed budget or amendment to a budget and the compensation that would be payable to Crawford thereunder is not approved by the Joint Committee or the Courts, Crawford may apply to the Courts for the termination of its appointment as Administrator upon providing 180 days notice to the Joint Committee and the Courts.

29. (1) Subject to subsection (2) where it is necessary or advisable for Crawford, in the course of its administration of the Plans, to seek the advice or direction of the Courts, Crawford shall be entitled to engage counsel for such purpose and shall be entitled to reimbursement from the Trust Fund of the reasonable fees and expenses of such counsel.

(2) Subsection (1) shall not apply to any legal fees or expenses incurred by Crawford regarding any proceeding in respect of any alleged negligence, wilful misconduct, or non-compliance with the terms of the Approval Orders of or by Crawford or the removal of Crawford as Administrator, unless the Joint Committee otherwise agrees or unless Crawford is substantially successful on the merits of such proceeding. If the Joint Committee agrees to reimburse such fees and expenses the Trust Fund may do so on a monthly basis as incurred by Crawford.

FORCE MAJEURE

30. Crawford shall not be liable for a failure or delay in the performance of its obligations in administering the Plans, including a failure or delay in respect of achieving the Service Performance Criteria:

(a) provided that such failure or delay:

(i) could not have been prevented by reasonable precautions, including pursuant to commercially reasonable business recovery planning; and

(ii) cannot reasonably be circumvented by Crawford through the use of alternate sources, work-around plans or other means; and

(b) if, and to the extent such failure or delay is caused, directly or indirectly, by fire, flood, earthquake, elements of nature or acts of God, acts of war, terrorism, riots, civil disorders, rebellions, strikes, lock-outs or labour or supply disruptions or revolutions or any other similar causes beyond Crawford's reasonable control;

(each, a **"Force Majeure Event"**).

31. Subject to sections 30 and 33, upon the occurrence of a Force Majeure Event, Crawford shall be excused from any further performance of those of its obligations in administering the Plans affected by the Force Majeure Event only for so long as:

(a) such Force Majeure Event continues; and

(b) Crawford continues to use commercially reasonable efforts to recommence performance whenever and to whatever extent possible without delay.

32. Crawford shall:

(a) immediately notify the Joint Committee by telephone (to be confirmed in writing within five days of the inception of such delay) of the occurrence of a Force Majeure Event; and

(b) describe, in such notice, in reasonable detail the circumstances causing the Force Majeure Event.

33. In the event such Force Majeure Event continues for a period of more than 60 days and Crawford is unable to perform all of its obligations in administering the Plans as a result thereof,

then the Joint Committee may, upon 15 days notice to Crawford, bring a motion for an Order terminating the appointment of Crawford as Administrator.

INDEMNIFICATION

34. Subject to section 36, Crawford shall be indemnified out of the Trust Fund for all liabilities, costs and expenses incurred in connection with its administration of the Plans other than for liabilities, costs and expenses incurred by Crawford:

(a) as a result of or in connection with negligence for which Crawford is liable under subsection 35(2); or

(b) willful misconduct; or

(c) which are covered or are required by the Approval Orders to be covered by insurance.

35. (1) Subject to subsections 35 (2) and (3) below, and to section 36, Crawford shall indemnify the Trust Fund for all liabilities, costs and expenses incurred by the Fund:

(a) as a result of or in connection with negligence for which Crawford is liable under subsection 35(2);

(b) willful misconduct; or

(c) which are covered or are required by the Approval Orders to be covered by insurance.

(2) Crawford's liability for all non willful acts, and negligence shall be limited to (a) repayment to the Trust Fund of any monies negligently paid out by Crawford together with interest thereon at the same rate as earned by the Trust Fund during the same period, which obligation shall not be limited as to amount and (b) any other direct damages for such negligence to a maximum of $20,000,000. Notwithstanding the foregoing, Crawford shall not be liable for errors in payment made to recipients to the extent that Crawford was acting in accordance with the standards to be expected of a commercially reasonable and prudent claims administrator.

(3) (a) At the end of each of (i) the six month period commencing on the Initial Period Confirmation Date, and (ii) the next following six-month period, the Joint Committee shall arrange for an audit of all payments made by Crawford during such six-month period (to be completed within 60 days following each such six-month period). If the Joint Committee, within 45 days after receiving such audit report, fails to advise Crawford that it takes exception to any payments made, then such payments will be deemed to be made without negligence; and

(b) thereafter, if within 45 days after its receipt of the annual audit report in respect of the administration of the Plans (to be prepared within 60 days following each relevant year end), the Joint Committee fails to advise Crawford that it takes exception to any payments made during the preceding year, then such payments will be deemed to be made without negligence.

36. (1) In no case shall the Trust Fund be liable to Crawford or Crawford liable to the Trust Fund for indirect damages, including any loss of interest (except as expressly provided in this Schedule) profit or revenue by the indemnified party or for any consequential, incidental, special, punitive or exemplary damages suffered by the indemnified party.

(2) The indemnification rights of Crawford provided for in Section 34 shall be the exclusive remedy of Crawford in respect of the administration of the Plans, and none of the Trust Fund (except to the extent provided in Section 34), the Trustee, the Auditors, the Class Action Counsel, the Class Members, the Courts, the FPT Governments, the Fund Counsel, the Investment Manager and the Joint Committee, including any persons serving or having served as same, shall have any liability to Crawford in respect of the subject-matter of the Approval Orders.

(3) The indemnification rights of the Trust Fund provided for in Section 35 shall be the exclusive remedy of the Trust Fund against Crawford in respect of the administration of the Plans, and (except to the extent provided in Section 35), Crawford shall have no liability to the Trust Fund in respect of the subject-matter of the Approval Orders.

37. Fund Counsel shall be entitled to assume control of the negotiation, settlement or defence of any claim brought against Crawford in connection with its administration of the Plans for which Crawford is indemnified.

38. Crawford shall cooperate with Fund Counsel so as to permit Fund Counsel to conduct such negotiation, settlement or defence and for this purpose shall preserve all relevant documents in relation to any such claims and allow Fund Counsel access to such documents.

39. In the event Crawford's appointment is not renewed and the term of its appointment expires, Crawford shall be indemnified out of the Trust Fund for its reasonable costs associated with the termination of employment for employees employed in the administration of the Plans.

40. In the event Crawford is removed as Administrator without cause, Crawford shall be indemnified out of the Trust Fund for all liabilities, fees, costs and expenses incurred by it as a result of such removal and to its indemnification rights pursuant to section 34. However, Crawford shall not be indemnified for any loss of income or profits.

41. In the event Crawford is removed as Administrator for cause, Crawford shall not be indemnified for any liabilities, costs or expenses incurred by it as a result of removal, provided however, that Crawford shall be entitled to receive out of the Trust Fund all of its fees and reimbursable expenses to the date of such termination and any rights of indemnification pursuant to section 34 which do not relate to the removal of Crawford as Administrator.

MISCELLANEOUS

42. (1) Subject to subsection (2) and except as provided in subsection 6(c)(v), Crawford shall not assign its rights or delegate its obligations under the Approval Orders except: (a) to a body corporate incorporated under the laws of Canada or the laws of the United States of America (or, respectively, any province or state thereof); (b) pursuant to a transaction whereby the successor is acquiring all or substantially all of the undertaking and assets of Crawford; (c) if the particulars of the successor and the terms of the transaction are, to the satisfaction of the

Courts, not materially disadvantageous to the administration of the Plans; and (d) if, prior to or contemporaneously with such transaction, the successor executes such instruments and consents to such orders of the Courts as the Courts determines to be necessary or advisable to constitute the successor as the Administrator.

(2) Subsection (1) shall not apply to Crawford contracting with one or more third parties for the provision to Crawford of constituent supplies or services necessary to the performance of the administrative obligations and not involving the management or control of all or a substantial part of the administration of the Plans.

43. (1) Reference is made to the lease (the **"Lease"**) of the premises (the **"Premises"**) in Ottawa at which the Claims Centre is to be situated. Crawford may use any part of the Premises or any furniture, furnishings or equipment located thereat, including computer hardware and software, for any purpose not related to the administration of the Plans, only:

(a) with the prior written consent of the Joint Committee, which consent may be withheld in the Joint Committee's unfettered discretion; or

(b) in compliance with subsections (2), (3), (4), (5) and (6) of this section.

(2) If Crawford wishes to utilize a portion of the Premises for purposes other than the exclusive administration of the Plans, Crawford shall submit an impact analysis to the Joint Committee detailing the reduction, if any, in the facilities and overhead factor used in determining Crawford's compensation for the administration of the Plans. Such analysis will utilize the following methodology:

(a) Presentation of the facilities and overhead costs associated with the personnel committed to the Claims Centre on a per capita basis;

(b) Presentation of the facilities and overhead costs associated with all personnel, regardless of project assignment, associated with the Claims Centre facilities, on a per capita basis; and

(c) Calculation of the proposed adjustment to the Claims Centre facility and overhead factor.

(3) If the Joint Committee does not accept Crawford's impact analysis, the Joint Committee shall be entitled to prepare its own impact analysis, following the same methodology as described in subsection (2), with respect to Crawford's proposal to use the Claims Centre for purposes other than the exclusive administration of the Plans. If such an analysis is prepared, then the Joint Committee shall provide a copy of such analysis to Crawford.

(4) In the event the Joint Committee and Crawford are not able to resolve the issue over the amount of the reduction in the facilities and overhead factor used in determining Crawford's compensation for the administration of the Plans, then the Joint Committee and Crawford, or failing which the Courts, shall select an arbitrator to resolve such issue. Such arbitrator's responsibility is to decide on the appropriate amount of the reduction in the facilities and overhead factor referred to above so that the fees and expenses allocated by Crawford to the

administration of the Plans does not have the result of subsidizing, through the Claims Centre facilities and overhead factor or otherwise, such other purpose as proposed by Crawford.

(5) If, upon any removal of Crawford as Administrator or upon any termination of its appointment as Administrator, Crawford is directed by the Joint Committee pursuant to subsection 7(a)(ii) of this Schedule to assign the Lease, to the extent assignable, to the Trustee or a new Administrator appointed by the Courts, then, subject to:

(a) the space and other Lease-related requirements for the ongoing administration of the Plans, as determined by the Joint Committee acting reasonably; and

(b) the Joint Committee and Crawford, both acting reasonably, agreeing upon other terms therefor (failing which same shall be determined by an arbitrator selected in accordance with subsection (4)),

Crawford shall be allowed the use of the balance of the Premises and other entitlements pursuant to the Lease and of any furniture, furnishings and equipment located thereat.

(6) No such alternate use of the Premises shall be permitted to interfere with, render more costly or otherwise adversely affect the continued fulfilment of the Service Performance Criteria or the administration of the Plans.

44. Any notice or other communication required or permitted to be given to any person pursuant to this Schedule shall be in writing and shall be:

(a) personally delivered;

(b) sent by prepaid registered and receipted mail;

(c) sent by same day or next day courier; or

(d) sent by facsimile or similar method of telecommunication, charges prepaid, and confirmed by prepaid registered mail.

Any notice so given shall be sent to the relevant person at the respective addresses provided for below:

If to Crawford:	Crawford Adjusters Canada 539 Riverbend Drive Kitchener, ON N2K 3S3
Attention:	Chief Executive Officer
With copies to:	The Garden City Group, Inc. Settlement Administration Specialists 1101 Stewart Avenue Garden City, NY 11530-4808
Attention:	President

If to the Joint Committee: to each of the individuals at the addresses set out below or to such other replacement members of the Joint Committee as may be appointed by the Courts.

Pierre Lavigne
200 – 440 Laurier Avenue West
Ottawa, ON K1R 7X6

Facsimile: 613-782-2445

JJ Camp
Camp Church & Associates
4th Floor, Randall Building
555 West Georgia Street
Vancouver, B.C. V6B 1Z5

Facsimile: 604-689-7554

Harvey T. Strosberg
Sutts, Strosberg LLP
600 – 251 Goyeau Street
P.O. Box 670, Stn. A
Windsor, ON N9A 6V4

Facsimile: 519-258-9527 or 519-258-9503

Bonnie Tough
Hodgson Tough Shields Desbrisay O'Donnell
550 – 36 Toronto Street
Toronto, ON M5C 2C5

Facsimile: 416-304-6406

45. Any person referred to in this Schedule may from time to time change its address and/or attention person by written notice to each of Crawford and the Joint Committee. Any notice or communication given by courier or personal delivery before 5:00 p.m. (recipient's time) on a Business Day shall be deemed to be received on the next following Business Day. Any notice sent by facsimile, if sent before 5:00 p.m. (recipient's time) on a Business Day shall be deemed to be received on the day of sending. Any notice sent by registered and receipted mail, if sent before 5:00 p.m. (sender's time) on a Business Day shall be deemed to have been received on the third Business Day following dispatch. Any notice or communication sent after 5:00 p.m. (sender's time) on a Business Day shall be deemed to have been received on the fourth Business Day following dispatch.

The Garden City Group, Inc.

The Garden City Group Canada
Class Action Administration Specialists
A Division of Crawford Adjusters Canada

SCHEDULE "B"

1986-1990 Hepatitis C Class Action Settlement
Year 1 Budget
For the period Apr 1, 2000 to Mar 31,2001

Printed 06/06/2000

1

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model
Year One Budget

April 1, 2000 to March 31, 2001

Dedicated Personnel Costs	*Note*	**Base Salary**	**Fringe**	**Total**	**# Personnel**	**Cost**
Total Ottawa Center Salary Expense					21.4	1,115,114
Other Compensation Related Expenses						
Overtime/Temporary Help	*3*					36,631
Staff Training & Education	*3*					33,453
Turnover	*3*					16,727
Performance Plan	*3*					111,511
Total Other Compensation Related Expense						198,322
Total Compensation excluding Fringe						1,313,436
Payroll Taxes and Benefit Costs	*4*					186,891
Total Compensation Expense						1,500,327
Gross mark-up						*28%*
Gross margin						*22%*
Total Dedicated Personnel Costs					**A**	**1,920,418**
Operational Costs	*5*					
Rent	*5a*					88,116
Occupancy	*5b*					26,266
Computer/network systems	*5c*					24,241
Communication	*5d*					149,099
Office equipment	*5e*					32,700
Office Supplies	*5f*					23,422
Mailing costs	*5g*					14,400
Transportation and Travel	*5h*					158,390
Printing & Copying	*5i*					71,099
Miscellaneous	*5j*					131,000
Bank Service Charges	*5k*					4,000
Total Operational Costs					**B**	**722,732**
TOTAL DEDICATED PERSONNEL AND OPERATIONAL COSTS FOR THE OTTAWA CENTRE					**C=A+B**	**2,643,151**

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model

			April 1, 2000 to March 31, 2001	
Indirect Support Costs				
Crawford Canada Corporate Support	6		D	390,000
Interest costs	7		E	-
TOTAL DIRECT PERSONNEL AND OPERATIONAL COSTS FOR THE OTTAWA CENTRE			F=C+D+E	3,033,151
Profit Component				420,091
Overall Net Margin				13.9%
NON-RECURRING, SPECIAL PROJECT AND/OR CAPITAL EXPENDITURES				
Assets/Capital Costs				
Assets / capital costs	*8*			
Navigant assets				217,570
Additional assets	*8a*			234,507
Lease costs	*8b*			23,800
Total Direct Purchases of Assets/Capital Costs				475,877
Garden City Software Modification				
Garden City US - Software Modification	*9*	Hourly rate	# Hours	Cost
(Year One only Costs)				
MIS Senior VP		275	300	82,500
Director Systems & Technology		200	100	20,000
Programmer/Analyst		185	1200	222,000
Technical Staff		150	700	105,000
President Emeritus		350	140	49,000
Administration Senior VP		300	60	18,000
Operations AVP		200	200	40,000
Quality Assurance		100	200	20,000
Sub-total				556,500
Additional software maintenance for year one (reduced beyond year one) *10*				166,800
Total Garden City software modification / maintenance fees for Year one				723,300

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model

	April 1, 2000 to March 31, 2001
Personal Assistance	
Other / external costs	
Personal assistance //	319,020
Independent medicals	
Computer / systems (if applicable)	
Sub-total	**319,020**
TOTAL NON-RECURRING, SPECIAL PROJECT AND/OR CAPITAL EXPENDITURES	**1,518,197**
GRAND TOTAL (INCLUDING OTHER PROJECT COSTS)	**4,551,347**
Monthly Amount (1/12 of Grand Total)	**379,279**

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model

April 1, 2000 to March 31, 2001

Assumptions

1. Year 1 (2000) = Apr 1, 2000 - Mar 31, 2001

2. Assumptions for # of Personal

Senior (project) Manager	Full time from Apr 1, 2000 - Mar 31, 2001
Project Manager (supervisor)	Full time from Apr 1, 2000 - Mar 31, 2001
Controller	Full time from Jun 1, 2000 - Mar 31, 2001 (10 Months) or .83 Equiv
MIS Manager	Full time from Apr 1, 2000 - Mar 31, 2001
Claims Assessors	2 Full time Equivs in April 2000 increasing to 4 in May 1, then to 5 by May 15, and then to 7 by Jun 15 and staying at this level through the rest of the year
Quality Assurance	On board as of end of 1st week in April and full time through Mar 31, 2001
Customer Service Reps (CSRs)	3 as of Apr 1, 2000 going to 4 half way through May and staying at 4 through the end of the year
Admin Support	0 in Apr, increasing to 2 in May, increasing to 5 in Jun staying at this level through the rest of the year
Admin Assistant	Full time from Apr 1, 2000 - Mar 31, 2001
Project Transition Managers	2 Managers for the first 6 Months during start up phase

3. Other Compensation Related Expense

Overtime/Temporary Help	5% of salary for Operations Staff only for peak period/absence coverage
Staff Training & Education	3% of salary for course fees/presentation and direct non-salary training expenses.
Turnover	1.5% of salary to cover terminations and recruitment cost.
Performance Plan	10% of salary based on standards from existing Crawford Plan.

4. Payroll Taxes & Benefits (Fringe)

		Employees	$/Employee	Total Exp
Canada Pension Plan (CPP) Estimated @ $1330 or Max/Employee		21.4	1,330	28,491
Employment Insurance (EI) Estimated at $1310 or Max/Employee		21.4	1,310	28,062
		Total Payroll	Rate	Total Exp
Employer Health Tax (EHT) 1.95% of Salary		1,279,982	1.95%	24,960
Registered Pension Plan (RPP) 5% of Salary		1,115,114	5.00%	55,756
Group Insurance (GI) 3.58% of Salary		1,115,114	3.58%	39,921
Workers Compensation $0.87 per $100		1,115,114	.87/100	9,701
Vacation	Cost Projection excluded			-
Total				186,891

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model
Assumptions (cont'd)

April 1, 2000 to March 31, 2001

5. Operational Costs

5a Monthly Rent Assumption	Yr 1 Expense
Base Rent	3,051
Common Area Expense	3,970
Parking	322
Total Monthly Assumption	7,343

5b Other Occupancy Cost Assumptions	Expense/Year
Security System @ $147/month	1,766
Revised Estimate is Off Site Storage 4282 cu ft @ $3/Cu Ft/yr & Transportation ($125/mo) to	16,500
Repairs, Maintenance, Janitor @ $300/mo	3,600
One Time Lease Adjustment (incurred upon transfer)	4,400
Total	26,266

5c Computer/Network Systems	
Frame Relay Connection 256K @ $1270/mo	15,241
ISP for Web Site @ $750/mo	9,000
Total	24,241

5d Communication Expense	Expense/Year
System Lease @ $725/Mo	8,700
Cellular/Pager = 2 Employees @$140/mo	3,360
Call Prompter Est @ 1200 Calls/Week * $0.15/Call	8,640
Access Lines @ $1265/mo	15,180
Long Distance 240 Mins/Day * 24 Lines @ $0.078/minute of use	113,219
Total Communication	149,099

5e Office Equipment	
Photocopier @ $525/mo	6,300
General Office Equipment Maintenance @$2,200/mo or 15% of Initial Investment	26,400
Total	32,700

5f Office Supplies	
Includes general office supplies, printer supplies, stationary, etc. estimated at $83.33/mo/Employee	21,422
Reference Material including Medical Reference Text, Income Tax, Legislation, etc.	2,000
Total	23,422

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model

April 1, 2000 to March 31, 2001

Assumptions (cont'd)

5g Mailing Costs		
Postage Meter @ 322/mo		3,864
Postage Expense $280/mo		3,360
Courier Expense @ $598/Mo		7,176
Total		14,400
5h Normal Transportation (excl Disbursements)		Year 1
Auto Monthly Allowance @$600/Mo & Credit Card (Gas) @$200/Mo		
Year 1 = 1 Full Time Mgr for entire year and 2 Mgrs for 6 months each		19,500
Transition Managers Travel and Accommodations (see below)		118,090
Travel & Out of Town Expense @ $400/wk		20,800
Total		158,390
Breakdown of travel and accommodations for transition managers		
Airfare - Regular	35,400	
Airfare - management team meetings and other travel	16,800	
Taxi	7,470	
Accommodations	42,850	
Per diem (meals)	15,570	
	118,090	
5i Printing & Copying		
External printing costs (application forms, letterhead, etc.)		60,145
Postage (regarding application mailing)		10,954
Total		71,099
5j Miscellaneous		
Insurance		6,000
Professional Services (Arthur Andersen)		60,000
Translation Services		50,000
Medical Consultant $250/hr * 60 Hrs		15,000
Total Miscellaneous		131,000

5k Bank Service Charges
Bank fees associated with Chequing Account

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model

April 1, 2000 to March 31, 2001

Assumptions (cont'd)

6. Corporate General and Admin

Ops Support / Management Oversight	100,000
Finance and Accounting	100,000
Information technology	100,000
Marketing	60,000
Human Resources	30,000
Total	390,000

7. Interest expense is assumed to be nil as all payments will be issued on a Net 30 basis with interest amount equivelant to prevailing pre-judgment interest rate established under the *Ontario Courts of Justice Act*.

8. Assets/Capital Costs purchased and owned by Crawford

8a Other Fixed Assets	Qty	Ea	
Workstations and other Office Equipment and Furniture			40,000
Fax	1 @	$3,219	3,219
Scanner	1 @	$24,605	29,605
21" Monitors	11 @	$1,609	17,697
French Keyboards	8 @	$59	468
Server	1		46,000
RAID Backup Hardware	1		30,000
Laptops	3 @	$4,310	12,930
CSU/DSU	1		1,200
Frame Relay Installation	1		1,966
NT Server Software	1		920
MS Office Licenses	26 @	$558	14,502
System Interface Development			36,000
Total			234,507

8b Leasehold	
Security System Installation	1,800
Projected Additional Leasehold Improvements	22,000
Total	23,800

9. Garden City costs are based on the estimated time to complete the software modification multiplied by discounted hourly rates. The net discount included in these figures is approximately $200,000.

In addition, Garden City will be required to maintain system updates to ensure compatibility with interacting software.

1986 - 1990 Hepatitis C Class Action Settlement
The Garden City Group Canada
Year-One Administration Budget Model

April 1, 2000 to March 31, 2001

Assumptions (cont'd)

10. Software Mainteneance
Ongoing Software Maintenance Costs to keep existing Application operating efficiently estimated
@ $13,900 mo or 30% of Initial Investment in year 1 166,800

11.

Personal Service	Qty	Hr/item	Tot Hours	Rate/Hr	Total $
Claims Alert Calls	5475	0.2	913	$120	109,500
Personal Assistance	57	2.0	114	$120	13,680
Field Investigations	204	3.0	612	$120	73,440
Regional Service Center Interview	376	2.5	940	$120	112,800
Attend Claimant Presentations/Meetings	12			$800	9,600
Total	6124		2579	$120	319,020

Note: Costs incurred to attend Claimant Meetings or Presentations are included in the "Personal Service" category.

CRAWFORD CANADA
HEPATITIS C CLASS ACTION SETTLEMENT
DISCUSSION OF ASSUMPTIONS
FOR THE PERIOD APRIL 1, 2000 TO MARCH 31, 2001
BASED ON A COST-PLUS BUDGET MODEL
(as of June 5, 2000)

The following is a discussion of the major assumptions that we have made in the preparation of our budget for the first year of the operations of the Ottawa Center (herein "the Center"). This discussion must be read in conjunction with the budget and the notes that accompany the budget.

1. TIME PERIOD

We have prepared this budget for the first year of the operation of the Centre, April 1, 2000 to March 31, 2001. The assumptions contained in this budget are applicable to this period only, and may require adjustment for subsequent years.

2. PERSONNEL

Our personnel costs are based an expectation that we will require a total of 22 staff members as follows:

Senior (project) Manager		Full time from Apr 1, 2000 - Mar 31, 2001.
Project Manager (supervisor)		Full time from Apr 1, 2000 - Mar 31, 2001.
Controller		Full time from Jun 1, 2000 - Mar 31, 2001 (10 Months).
MIS Manager		Full time from Apr 1, 2000 - Mar 31, 2001.
Claims Assessors		2 Full time staff in April 2000 increasing to 4 at May 1, 2000, then to 5 by May 15, 2000 and then to 7 by Jun 15, 2000.
Quality Assurance		Commencing employment as of the end of the 1st week in April, 2000 and full time through Mar 31, 2001
Customer Service Reps (CSRs)		3 full time staff members as of Apr 1, 2000 going to 4 half way through May and staying at 4 through the end of the year.
Admin Support		0 in Apr, 2000 increasing to 2 in May, 2000, increasing to 5 in Jun, 2000 and staying at this level through the rest of the year.
Admin Assistant		Full time from Apr 1, 2000 - Mar 31, 2001
Project Transition Managers		2 Managers for the first 6 Months during start-up phase

Staffing Levels and Volume of Claims in Year 1

In establishing the required staffing levels and associated costs of the Center in the first year of operations (defined as April 1, 2000 to March 31, 2001), we have made certain assumptions regarding the expected volume of claims (allocated by type of claim) and processing time per claim. Given that the claims processing activities will generally be labour intensive, the volume of claims expected to be received by the Center is an important consideration for establishing required staffing levels and associated costs.

In arriving at the expected volume of claims, we have considered and relied upon the following:

- Statistics and assumptions included in the report prepared by Eckler Partners Ltd. dated July 9, 1999 (the "Eckler Report");
- The analysis of Robert S. Remis dated July 6, 1999 (the "Remis Report");
- The report prepared by the Canadian Association for the Study of the Liver ("CASL") (the "CASL Report"); and,
- Discussion with Ms. Sharon Matthews of the Joint Committee.

The foregoing reports generally established the probable (on a statistical basis) number of "valid" claims that would be eligible to receive benefits from the trust fund. However, the reports do not specifically estimate the number of "invalid" claims that the centre will have to process. As a result, we have made a conservative assumption regarding these claims below.

Based on the foregoing reports, we have considered the following assumptions regarding the possible total number of valid claims that could be expected to be received at the Center. In particular, we have relied primarily on the Eckler Report and considered any discrepancies between the other reports in our overall sensitivity analysis:

	As at January 1999
Total Cohort Size of "infected" transfusees	15,707
Assumed deaths (non-HCV related)	7,527
Assumed deaths (HCV related)	76
Surviving Cohort of infected transfusees	8,104[1]

[1] The Remis Report estimates a lower surviving cohort of 6,584.

Primarily Infected Persons

As shown above, the Eckler Report estimates that there could be approximately 8,104 HCV infected transfusees. However, this figure considers only transfused victims and not hemophiliac claims, which we understand could be approximately 1,500 to 1,800 (Eckler Report). Accordingly, the total possible claims from primarily infected individuals could be approximately 10,000 over the life of the settlement.

In estimating the required personnel costs for year one, we must make assumptions regarding:

- The number of claims that will actually be received from these individuals (i.e. individuals may not file claims or may not be aware of their infection);
- The number of claims that will be received in the first year;
- The number of claims that will not be considered valid (i.e. denied claims due to reasons such as transfusion during periods outside the relevant period of 1986 to 1990).

We have conservatively estimated that 80% of the possible claimants will actually submit claims over the life of the settlement and that as much as three quarters of these claims will be received in the first year. That is, we have estimated that of the total possible valid claims of 10,000, approximately 6,000 claims will be received in year one (10,000 X 80% X 75%).

Types of claims

Consistent with the Settlement Agreement, differing levels of compensation are to be provided based primarily on the progression of the infection. Therefore, depending on the stage of disease development, claimants will receive varying settlement amounts. Claimants in a more advance stage of disease development will be required to submit additional information that will be reviewed by Centre personnel. Based on the Eckler Report, as at January 1, 1999, the distribution of the 8,104 possible infected transfusees is as follows:

Disease stage	Number	%
Cleared virus	1,621	20%
PCR positive	2,271	28%
Stage 1 – Non-bridging fibrosis	1,501	18%
Stage 2 – Non-bridging fibrosis	1,238	15%
Bridging fibrosis	790	10%
Cirrhosis	544	7%
Decomp/Cancer	140	2%
	8,104	**100%**

We have assumed that claimants in disease stages beyond "Stage 1 – Non-bridging fibrosis" would likely require additional investigation/claim beyond the claimants who clear the virus or test PCR positive. The relative proportions of this broad category of claims are approximately 50/50. Applying a similar portion to the estimated year one possible "valid" claims of 6,000 would indicate 3,000 advanced claims.

Secondarily Infected Persons (Derivative claims)

The Eckler Report estimates the total possible claims from secondarily infected person (i.e. sexually transmitted or mother-infant infection) to be approximately 189[2]. Applying the same proportions for year one claims implies a possible year one claim total for secondarily infected persons of approximately 110. We have considered a possible claim amount of 200 to be conservative.

Intrinsically Ineligible Claims and Denials

In addition to the "valid" claims, the Ottawa center personnel will be required to review and process claims that are intrinsically ineligible (e.g. individuals not transfused during the relevant period) or ultimately denied with further investigation. We understand that certain studies have indicated a denial claim figure as low as 10%. However, our experience has suggested that this figure could be significantly higher. We have conservatively estimated the denials to be as high as 2,000. These claims, although ultimately denied, still require a basic level of processing time for data capture, assembly and customer service.

[2] The Remis Report estimates this figure at 210

Death Claims

The Eckler Report considers possible death claims from HCV infected transfusees to be approximately 76. However, this number is likely larger if we consider that a greater number of Hemophiliacs have died. Furthermore, there will likely be additional claims for non-HCV related deaths by individuals "hoping" to convince the administrator that the death was caused by HCV. Based on the foregoing, we have estimated that year one death claims (valid and invalid) could be approximately 1,300 (based on approximately 15% to 20% of the total HCV infected transfusees deaths of approximately 7,600).

Advanced Claims

Individuals who progress to the next level of disease are entitled to receive additional settlement, which will require additional investigation by the administrator. Given that the Eckler Report assumes a progression rate of 7.5 years, it is unlikely that the Center will receive advanced claims in the first year of operations.

Summary

Based on the foregoing discussion, we have assumed the following claim volumes for year one:

Total valid level 1 claims	3,000
Total valid advanced claims	3,000
Secondary claims	200
Denials	2,000
Death claims	1,300
Total volume of claims	9,500

We believe the foregoing to be a conservative estimate but consistent with the significant volume of approximately 6,500 applications that were mailed recently by the Centre staff.

Claims processing time

We have estimated the processing procedures and associated time as follows based on our understanding of the Settlement Agreement and our experience in claims processing:

Function	Hours	Volume	Total Hours
Initial Claim Submission			
Preparation and scanning	0.33	9,500[3]	3,135
Data capture	0.25	9,500	2,375
Data review and message code assignment – "Intrinsically ineligible" claims	0.25	3,200[4]	800
Data review and message code assignment – "Valid"	1.00	6,300	6,300
Letter generation in weekly batches	0.05	9,500	475
Letter control and mailing	0.05	9,500	475
Sub-total initial claim submission			13,560
Advance claim / additional forms / letter responses			
Preparation and scanning	0.15	4,500	675
Data capture	0.10	4,500	450
Data review and message codes	1.00	3,000	3,000
Data review and special functions	1.00	375[5]	375
Sub-total advance claim			4,500
Grand total			18,060

We have assumed that claims processors and administrative staff would perform the foregoing procedures. Based on an hourly work year of approximately 1,750 hours, the minimum required number of claims processors and administrative support staff is approximately 10.3. As shown in the attached budget, we have budgeted for approximately 6.3 full-time equivalent claims processors and 4.5 administrative support staff (a total of 18,900 hours in year one). We believe that the additional capacity of 740 hours represents sufficient staff coverage for possible contingencies, unforeseen increases in claim volume or complexity, and other claims involving family members.

[3] Assuming an average of 40 to 50 pages per claim.

[4] Estimated as 2,000 denials and 1,200 denied death claims.

[5] Based on 12.5% of advanced claims opting for income replacement benefits (as per Eckler)

The Garden City Group Canada
Class Action Administration Specialists
A Division of Crawford Adjusters Canada

Annex B

5 June 2000

Crawford Some Key Budget Points of Interest

1. The Costs-Plus budget model includes the assumptions and estimates upon which the budget is based. The "Crawford Hepatitis Class Action Settlement Discussion of Assumptions for the Period April 1, 2000 to March 31, 2000 is attached for approval.

2. Legal fees for the Quebec proceedings held in January 2000 are not included.

3. The budgeted amount ($723,000) will cover IT work required to process tasks in accordance with the Settlement Agreement as it is drafted today. Assuming that no changes are made to Settlement Agreement, modifications and upgrades, which would increase system, capability or address new requirements would be "extra" but functional capability maintenance is included.

4. "Claimant Meetings/Assisting with Completing the Claim Forms" costs will be "expensed" under the personal assistance budget item. For tracking purposes, please note that we broke this cost down to equal roughly $9,600 of the total personal assistance budget item.

5. Interest is not included in the budget. In other words, interest will not be prepaid. Monthly payments to Crawford, which are 30 days overdue, will be paid as per the interest rate stated on the invoice (prevailing pre-judgment interest rate established under the *Ontario Courts of Justice Act*).

6. We have budgeted $4,000 for banking fees relating to the Royal Bank chequing account for this first fiscal year. It is understood that this expense will be a complete flow-through from Crawford to the Fund.

DIANNE LOUISE PARSONS et al.
JAMES KREPPNER et al.
Plaintiffs

THE CANADIAN RED CROSS SOCIETY et al.
Defendants

Court File No. 98-CV-141369 cp
98-CV-146405 cp

ONTARIO
SUPERIOR COURT OF JUSTICE

PROCEEDINGS COMMENCED AT TORONTO

ORDER

SUTTS, STROSBERG LLP
Barristers and Solicitors
600 Westcourt Place
251 Goyeau Street
Windsor ON N9A 6V4

HARVEY T. STROSBERG, Q.C.
Tel: (519) 258-9333
Fax: (519) 258-9527

FILE: 44-900-000
REF: HTS/sw

THE ATTACHED IS EXHIBIT "E" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

	TRUSTEE	INVESTMENT MANAGERS	INVESTMENT CONSULTANTS	ACTUARIES GENERAL AND INVESTMENT ADVICE	ACTUARIES FINANCIAL SUFFICIENCY	AUDITORS AUDIT SERVICES ONLY	CLAIMS ADMINISTRATOR	JOINT COMMITTEE GENERAL	JOINT COMMITTEE SUFFICIENCY	FUND COUNSEL
YEAR 1 - 16 MONTHS TO MARCH 31, 2001	$108,937	$192,615	$56,604	$22,079		$45,000	$4,267,151	$1,200,000		$940,000
YEAR 2 TO MARCH 31, 2002	$103,824	$203,573	$56,000[1]			$45,000	$4,574,373	$774,588[2]		$661,595
YEAR 3 TO MARCH 31, 2003	$120,000	$183,074		$28,194	$277,210	$66,233	$3,938,174	$1,021,380[2]		$614,806
YEAR 4 TO MARCH 31, 2004	$106,400	$181,069		$58,901	$31,702	$61,000	$3,254,633	$632,900		$567,530
YEAR 5 TO MARCH 31, 2005	$95,800	$184,484		$52,540		$61,000	$2,594,307	$1,019,334[2]		$473,150
YEAR 6 TO MARCH 31, 2006	$93,700	$188,317		$55,235[3]		$63,000	$2,298,202[3]	$608,252	$380,537[3]	$538,998
YEAR 7 - 9 MONTHS TO DECEMBER 31, 2006	$70,000	$142,666		$32,254	$484,785	$70,200	$1,695,261	$438,501	$78,087	$291,220
YEAR 8 TO DECEMBER 31, 2007	$90,994	$192,421		$45,678		$67,200	$1,955,447	$295,967	$50,676	$326,301
YEAR 9 TO DECEMBER 31, 2008	$130,665	$182,084		$47,719	$297,055	$70,000	$1,261,316	$220,080	$177,994	$136,287

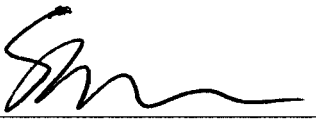
[1] Removed as Investment Consultant with Eckler approved to provide investment advice going forward.
[2] Includes sufficiency which were not delineated.
[3] Not including services reimbursed by federal government relating to assisting with its actuarial work

	TRUSTEE	INVESTMENT MANAGERS	INVESTMENT CONSULTANTS	ACTUARIES GENERAL AND INVESTMENT ADVICE	ACTUARIES FINANCIAL SUFFICIENCY	AUDITORS AUDIT SERVICES ONLY	CLAIMS ADMINISTRATOR	JOINT COMMITTEE GENERAL	JOINT COMMITTEE SUFFICIENCY	FUND COUNSEL
YEAR 10 TO DECEMBER 31, 2009	$98,186	$165,900		$46,519	$62,586	$74,530	$1,144,429	$304,832	$58,839	$144,253
YEAR 11 TO DECEMBER 31, 2010	$95,472	$171,351		$54,687	$153,082	$76,426	$1,172,987	$505,531	$64,462	$80,691
YEAR 12 TO DECEMBER 31, 2011	$94,425	$189,431		$22,780	$647,883	$78,000[4]	$761,212	$445,478	$306,258	$144,732
YEAR 13 TO DECEMBER 31, 2012	$96,247	$202,152		$26,785	$223,744	$81,000[4]	$731,739	$573,994	$208,282	$142,843
YEAR 14 TO DECEMBER 31, 2013	$94,879	$229,930[5]		$49,045	$41,348	$81,000[4]	$758,617	$740,596	$182,699	$267,512
TOTALS	**$1,399,529**	**$2,609,067**	**$112,604**	**$542,416**	**$2,219,395**	**$939,589**	**$30,407,848**	**$8,781,433**	**$1,507,834**	**$5,329,918**

1400202

[4] Estimate after deducting costs for preparation of financial statements.
[5] Including special project fees for duration matching.

THE ATTACHED IS EXHIBIT "F" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016



COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Schedule "A"

Court approved protocol

REVISION: OCTOBER 2010

REVISED COURT APPROVED PROTOCOL FOR MEDICAL EVIDENCE FOR SECTION 4.01(1) AND 4.01(2) OF ARTICLE 4 OF THE TRANSFUSED HCV PLAN AND THE HEMOPHILIAC HCV PLAN

This Protocol sets out the acceptable medical evidence for Section 4.01(1) and 4.01(2) of Article 4 of the applicable Plan.

DISEASE LEVEL 1
To be entitled to the fixed payment provided for at Section 4.01(1)(a) of the applicable Plan, the Approved HCV Infected Person will have delivered to the Administrator the following:

a. a satisfactorily completed TRAN2/HEMO2 Treating Physician Form; and

b. a positive HCV Antibody Test in compliance with the SOP - Criteria for Acceptable HCV Antibody Test and PCR Test.

DISEASE LEVEL 2
To satisfy the medical evidence requirement at Section 4.01(1)(b) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator the following:

a. a satisfactorily completed TRAN2/HEMO2 Treating Physician Form; and

b. a positive PCR Test in compliance with the SOP -Criteria for Acceptable HCV Antibody Test and PCR Test.

DISEASE LEVEL 3
To satisfy the medical evidence requirement at Section 4.01(1)(c) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator a satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has either:

a. developed fibrous tissue in the portal areas of the liver with fibrous bands extending out from the portal areas but without any bridging to other portal tracts or to central veins ("non-bridging fibrosis") as confirmed by a copy of a pathology report of a liver biopsy or by a positive result on Fibroscan (Elastography) ;

b. undergone one of the following types of Compensable HCV Drug Therapy:

   i. interferon therapy;

   ii. combination interferon and ribavirin therapy;

   iii. interferon combined with a drug other than ribavirin;

   iv. ribavirin combined with a drug other than interferon; or

c. met or meets the following protocol for Compensable HCV Drug Therapy:

   i. the HCV Infected Person is HCV RNA positive as confirmed by a copy of a PCR Test in compliance with the SOP-Criteria for Acceptance of HCV Antibody Test and PCR Test;

ii. the HCV Infected person has medically demonstrated evidence of fibrotic changes to the liver as confirmed by a copy of a pathology report of a liver biopsy or by a positive result on Fibroscan (Elastography); or

iii. the HCV Infected Person's ALTs were elevated 1.5 x normal for 3 months or more as confirmed by liver function test reports provided; and

iv. the infection with HCV materially contributed to the elevated ALTs as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

d. in circumstances where the above protocol is not met:

i. certification by a gastroenterologist, hepatologist, infectious disease specialist or internist that:

a. the Approved HCV Infected Person has met or meets a protocol for Compensable HCV Drug Therapy consistent with the treatment decision factors set out in the most recent CASL Consensus Guidelines for the Management of Hepatitis C, including some HCV disease indicator(s) in addition to a positive PCR test;

b. and which the certifying physician asserts is within generally accepted medical standards for recommending treatment.

DISEASE LEVEL 4
To satisfy the medical evidence requirement at Section 4.01(2) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator a satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has developed fibrous tissue in the portal areas of the liver with fibrous bands bridging to other portal areas or to central veins but without nodular formation or nodular regeneration ("bridging fibrosis") as confirmed by a copy of a pathology report of a liver biopsy.

DISEASE LEVEL 5
To satisfy the medical evidence requirement at Section 4.01(1)(d) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator either:

1. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person:

1. has developed fibrous bands in the liver extending or bridging from portal area to portal area with the development of nodules and regeneration ("cirrhosis") as confirmed by:

i. a pathology report of a liver biopsy;

ii. a Fibroscan report (Elastography);

iii. an Ultrasound report;

iv. an MRI report;

v. a CT Scan report; or

2. in the absence of a liver biopsy or Fibroscan, has been diagnosed with cirrhosis based on:

i. three or more months with:

A. an increase in all gamma globulins with decreased albumin on serum electrophoresis as reported on a serum electrophoresis test provided;

B. a significantly decreased platelet count as reported on laboratory reports provided; and

C. an increased INR or prothrombin time as reported on laboratory reports provided;
none of which are attributable to any cause other than cirrhosis; and

ii. a finding of hepato-splenomegaly, supported by a copy of an ultrasound report, an MRI report or a CT scan report of an enlarged liver and spleen, and one or more of the following peripheral manifestations of liver disease, none of which are attributable to any cause other than cirrhosis:

A. gynecomastia;

B. testicular atrophy;

C. spider angiomata;

D. protein malnutrition;

E. palm or nail changes characteristic of liver disease; or

iii. one or more of the following, none of which are attributable to any cause other than cirrhosis:

A. portal hypertension evidenced by:

1. an enlarged spleen which is inconsistent with portal vein thrombosis as confirmed by a copy of an ultrasound report; or

2. abnormal abdominal and chest wall veins as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

B. esophageal varices as reported on an endoscopic report ;

C. ascites as reported on an ultrasound report, an MRI report or a CT Scan report .

OR

2. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with porphyria cutanea tarda:

a. which failed to respond to one or more of the following treatments:

i. phlebotomy;

ii. drug therapy - specifying the therapy;

iii. Compensable HCV Drug Therapy; and

b. which is causing significant disfigurement and disability, a description of which is provided;
as confirmed by a 24 hour urine laboratory test report provided and a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the findings unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

OR

3. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has thromobocytopenia unresponsive to therapy based on one or more of the following:

a. a platelet count below 100 x 109 with:

i. purpura or other spontaneous bleeding; or

ii. excessive bleeding following trauma;
as confirmed by a copy of a laboratory report and a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting either finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

b. a platelet count below 30 x 109, as reported on a laboratory report provided.

OR

4. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with glomerulonephritis not requiring dialysis which is consistent with infection with HCV and copies of the following:

a. a pathology report of a kidney biopsy which reports a finding of glomerulonephritis; and

b. a consultation or other report of a nephrologist confirming that the HCV Infected Person has glomerulonephritis not requiring dialysis which is consistent with infection with HCV unless the Treating Physician is a nephrologist.

DISEASE LEVEL 6
To satisfy the medical evidence requirement at Section 4.01(1)(e) of the applicable Plan, the Approved HCV Infected Person must deliver to the Administrator either:

1. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has had a liver transplant together as confirmed by a copy of an operative report of the transplant.

OR

2. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has decompensation of the liver based on a finding of one or more of the following:

    a. hepatic encephalopathy as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

    b. bleeding esophageal varices as confirmed by a copy of an endoscopic report;

    c. ascites as confirmed by a copy of an ultrasound report, MRI report or CT Scan;

    d. subacute bacterial peritonitis as confirmed by a copy of a laboratory report showing a neutrophil count of greater than 150×10^9 per ml in the ascitic fluid and/or positive ascitic culture;

    e. protein malnutrition as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

    f. another condition a description of which is provided as confirmed by a copy of a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

    OR

3. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with hepatocellular cancer based on one or more of the following:

    a. a pathology report of a liver biopsy which reports hepatocellular cancer;

    b. an alpha feto protein blood test report and a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist;

    c. a report of a CT scan or MRI scan of the liver confirming hepatocellular cancer.

    OR

4. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with B-Cell lymphoma as confirmed by a copy of a consultation or other report of an oncologist or hematologist supporting the finding unless the Treating Physician is an oncologist or hematologist.

    OR

5. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with symptomatic mixed cryoglobulinemia and copies of:

    a. (a) the results of a blood test demonstrating elevated cryoglobulins; and

b. (b) a consultation or other report of a gastroenterologist, hepatologist, infectious disease specialist or internist supporting the finding unless the Treating Physician is a gastroenterologist, hepatologist, infectious disease specialist or internist.

OR

6. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with glomerulonephritis requiring dialysis which is consistent with infection with HCV and copies of the following:

   a. a pathology report of a kidney biopsy which reports a finding of glomerulonephritis; and

   b. a consultation or other report of a nephrologist confirming that the HCV Infected Person has glomerulonephritis requiring dialysis which is consistent with infection with HCV unless the Treating Physician is a nephrologist.

   OR

7. A satisfactorily completed TRAN2/HEMO2 Treating Physician Form which indicates that the HCV Infected Person has been diagnosed with renal failure and copies of:

   a. laboratory reports of serum creatinine and serum urea supporting the diagnosis; and

   b. a consultation or other report of a nephrologist supporting the diagnosis unless the Treating Physician is a nephrologist.

Notes:

DISEASE LEVEL 3
[1]Note: The Administrator shall:

a. accept the pathology report or Fibroscan report as evidence of non-bridging (or more severe) fibrosis if the pathology report or Fibroscan report is reported in terms which on their face are consistent with or exceed (in terms of severity of fibrosis) non-bridging fibrosis;

b. accept the pathology report or Fibroscan Report as evidence of non-bridging (or more severe) fibrosis although the pathology report or Fibroscan report is not reported in such terms, if the Treating Physician is a pathologist, gastroenterologist, hepatologist, infectious disease specialist or internist; or

c. seek the assistance of a pathologist to interpret the pathology report. If necessary, the advising pathologist will request the pathology slides to make the determination.

DISEASE LEVEL 4
[2]Note: The Administrator shall:

a. accept the pathology report as evidence of bridging (or more severe) fibrosis if the pathology report is reported in terms which on their face are consistent with or exceed (in terms of severity of fibrosis) bridging fibrosis;

b. accept the pathology report as evidence of bridging fibrosis although the pathology report is not reported in such terms, if the Treating Physician is a pathologist, gastroenterologist, hepatologist, infectious disease specialist or internist; or

c. seek the assistance of a pathologist to interpret the pathology report. If necessary, the advising pathologist will request the pathology slides to make the determination.

DISEASE LEVEL 5

[3]Note: The Administrator shall:

a. accept the pathology report, Fibroscan report, CT Scan report, Ultrasound report or MRI report as evidence of cirrhosis if the applicable report is reported in terms which on their face are consistent with or exceed (in terms of severity of fibrosis) cirrhosis;

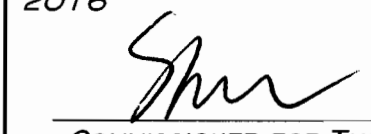
b. accept the pathology report, Fibroscan report, CT Scan report, Ultrasound or MRI report as evidence of cirrhosis although the pathology report is not reported in such terms, if the Treating Physician is a pathologist, gastroenterologist, hepatologist, infectious disease specialist or internist; or

c. seek the assistance of a pathologist to interpret the pathology report. If necessary, the advising pathologist will request the pathology slides to make the determination.

DISEASE LEVEL 6

[4]Note: In the event that the Treating Physician specifies another condition at 2f), the Administrator shall seek the advice of a gastroenterologist, hepatologist, infectious disease specialist or internist as to whether the diagnosis of decompensation of the liver would be generally accepted by the medical community in those circumstances.

THE ATTACHED IS EXHIBIT "G" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016



COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

The 1986-1990 Hepatitis C Claims Centre
PO Box 2370, Station D
Ottawa (Ontario) K1P 5W5
Canada
Tel: 1 877 434-0944
www.hepc8690.ca

TRAN 2

Treating Physician Form

Strictly Private and Confidential

CLAIMANT PLEASE AFFIX HERE ONE OF THE PREPRINTED LABELS PROVIDED

* If you do not have the labels, call 1 877 434-0944 for instructions.

CORRECTIONS ONLY

Write any name, address or telephone number corrections below, if any corrections are necessary.

SECTION A – HCV INFECTED PERSON

1.

First Name	Middle Name/Initial	Last Name	
Home Address	**City/Municipality**	**Province/Territory**	**Postal Code**
Date of Birth (DD/MM/YYYY)	**Provincial/Territorial Health Number**	**Province/Territory of Health Plan**	
/ /	- -		

SECTION B – TREATING PHYSICIAN

2.

First Name	Middle Name/Initial	Last Name	
Name of Facility	**Mailing Address**		
City/Municipality	**Province/Territory**	**Postal Code**	
Work Phone	**Facsimile**	**E-Mail Address**	**Specialty**
( ) -	( ) -		

SECTION C – HCV ANTIBODY TEST AND/OR PCR TEST

Please complete this section even if the HCV Infected Person has died.

Each HCV Infected Person must have either a positive HCV Antibody Test or a positive PCR Test acceptable to the Administrator to be eligible for compensation. **These tests also establish entitlement to one of the two lower compensation disease levels. (The Administrator will arrange for a PCR Test to be performed if it is necessary to determine a disease compensation level and if an acceptable test has not already been performed.)**

Please check each box that applies and attach the most recent laboratory report.

3. ☐ **DISEASE LEVEL 1** The HCV Infected Person has the Hepatitis C antibody present in his or her Blood as demonstrated by the HCV Antibody Test performed.

4. ☐ **DISEASE LEVEL 2** The HCV Infected Person has the Hepatitis C virus present in his or her Blood as demonstrated by the PCR Test performed.

SECTION D – ADVANCED DISEASE LEVELS

Complete this section even if the HCV Infected Person has died **on or after** January 1, 1999. If the HCV Infected Person died before January 1, 1999 go to Section E – Patient History.

The disease levels are listed below in descending order of severity. Please **fill out the most severe disease level that applies** to the HCV Infected Person and then go to Section E – Patient History.

NOTE: The request for consultation or other reports from any particular specialty is a request for existing reports only. This is <u>not</u> a request for a specialist or other treating physician to prepare a report at this time.

Refer to the Form Instructions for definitions.

DISEASE LEVEL 6

There are seven medical conditions listed below, any one of which would qualify the HCV Infected Person at this disease level. Check each box that applies to the HCV Infected Person's medical condition, **attach the documentation specified** and provide the requested opinion.

5. ☐	The HCV Infected Person has had a **liver transplant** (attach the operative report).
6. ☐	The HCV Infected Person has been diagnosed with **decompensation of the liver** based on a finding of one or more of the following: ☐ hepatic encephalopathy (attach a consultation or other report of a gastroenterologist, hepatologist or internist supporting the finding); ☐ bleeding esophageal varices (attach the endoscopic report); ☐ ascites (attach the ultrasound report); ☐ subacute bacterial peritonitis (attach the laboratory report with a white cell count of greater than 150 x 10^9 per ml in the ascitic fluid); ☐ protein malnutrition (attach a consultation or other report of a gastroenterologist, hepatologist or internist supporting the finding); ☐ another condition (specify the condition and attach a consultation or other report of a gastroenterologist, hepatologist or internist supporting the finding) _____.
7. ☐	The HCV Infected Person has been diagnosed with **hepatocellular cancer** based on: ☐ a liver biopsy (attach the pathology report); ☐ an alpha feto protein Blood test (attach the laboratory report and a consultation or other report of a gastroenterologist, hepatologist or internist supporting the diagnosis); or ☐ a liver scan (attach the CT scan or MRI scan report).
8. ☐	The HCV Infected Person has been diagnosed with **B-cell lymphoma** (attach a consultation or other report of an oncologist or hematologist supporting the diagnosis).
9. ☐	The HCV Infected Person has been diagnosed with **symptomatic mixed cryoglobulinemia** (attach a laboratory report confirming elevated cryoglobulins and a consultation or other report of a gastroenterologist, hepatologist or internist supporting the diagnosis).
10. ☐	The HCV Infected Person has been diagnosed with **glomerulonephritis requiring dialysis** based on a kidney biopsy (attach the pathology report and a consultation or other report of a nephrologist supporting the diagnosis and indicating it is consistent with the HCV infection).
11. ☐	The HCV Infected Person has been diagnosed with **renal failure** (attach laboratory reports of serum creatinine and serum urea and a consultation or other report of a nephrologist supporting the diagnosis).

It is my opinion that the HCV Infected Person's infection with <u>HCV materially contributed</u> to his or her Disease Level 6 medical condition.	**Yes** ☐ **No** ☐

If the HCV Infected Person has a Disease Level 6 condition and you have completed the above portion of this Form, go to Section E – Patient History.

DISEASE LEVEL 5

There are four medical conditions listed below, any one of which would qualify the HCV Infected Person at this disease level. Check each box that applies to the HCV Infected Person's medical condition, attach the documentation specified and provide the requested opinion.

12. ☐ The HCV Infected Person has been diagnosed with **cirrhosis** based on a liver biopsy demonstrating fibrous bands in the liver extending or bridging from portal area to portal area with the development of nodules and regeneration (attach the pathology report).
In the absence of a liver biopsy, the HCV Infected Person has been diagnosed with **cirrhosis** based on:

☐ three or more months with an increase in all gamma globulins with decreased albumin on serum electrophoresis and a significantly decreased platelet count and an increased INR or prothrombin time none of which are attributable to any cause other than cirrhosis (attach a serum electrophoresis test and other laboratory reports supporting each finding);

AND

☐ hepato-splenomegaly (attach the ultrasound report) with peripheral manifestations of liver disease such as the following, none of which are attributable to any cause other than cirrhosis:

☐ gynecomastia ☐ testicular atrophy ☐ spider angiomata

☐ protein malnutrition ☐ palm or nail changes characteristic of liver disease

OR

One or more of the following, none of which are attributable to any cause other than cirrhosis**:**

☐ Portal hypertension confirmed by:

☐ an enlarged spleen which is inconsistent with portal vein thrombosis (attach the ultrasound report);

☐ abnormal abdominal and chest wall veins (attach a consultation or other report of a gastroenterologist or internist supporting the finding);

☐ esophageal varices (attach the endoscopic report); or

☐ ascites (attach the ultrasound report).

13. ☐ The HCV Infected Person has been diagnosed with **porphyria cutanea tarda** (attach a 24 hour urine laboratory test report)

☐ which has failed to respond to the treatments attempted as follows:

☐ phlebotomy;

☐ drug therapy (specify the therapy) _____; or

☐ interferon and/or ribavirin alone or in combination with each other or with other drugs (Compensable HCV Drug Therapy);

☐ and which is causing significant disfigurement and disability as follows (describe disfigurement and disability):

_____

_____

_____

(attach a consultation or other report of a gastroenterologist, hepatologist or internist confirming the diagnosis).

14. ☐ The HCV Infected Person has **thrombocytopenia** unresponsive to therapy based on one or more of the following:

☐ a platelet count below 100 x 10^9 (attach the laboratory report) with:

☐ purpura or other spontaneous bleeding; or

☐ excessive bleeding following trauma (attach a consultation or other report of a **gastroenterologist, hepatologist or internist** supporting either finding);

☐ a platelet count below 30 x 10^9 (attach the laboratory report).

15. ☐ The HCV Infected Person has **glomerulonephritis not requiring dialysis** based on a kidney biopsy (attach a pathology report and a consultation or other report of a nephrologist supporting the diagnosis and indicating it is consistent with infection with HCV).

It is my opinion that the HCV Infected Person's infection with <u>HCV materially contributed</u> to his or her Disease Level 5 condition.	**Yes** ☐ **No** ☐

If the HCV Infected Person has a Disease Level 5 condition and you have completed the above portion of this Form, go to Section E – Patient History.

DISEASE LEVEL 4

The medical condition listed below would qualify the HCV Infected Person at this disease level. Check the box if it applies to the HCV Infected Person's medical condition and attach the documentation specified.

16. ☐ The HCV Infected Person has **bridging fibrosis** based on a liver biopsy demonstrating fibrous tissue in the portal areas of the liver with fibrous bands bridging to other portal areas or to central veins but without nodular formation or nodular regeneration (attach the pathology report).

If the HCV Infected Person has a Disease Level 4 condition and you have completed the above portion of this Form, go to Section E – Patient History.

DISEASE LEVEL 3

There are three criteria listed below, any of which would qualify the HCV Infected Person at this disease level. Check each box that applies to the HCV Infected Person's medical condition, attach the documentation specified and provide the requested opinion.

17. ☐ The HCV Infected Person has **non-bridging fibrosis** based on a liver biopsy demonstrating fibrous tissue in the portal areas of the liver with fibrous bands extending out from the portal areas but without any bridging to other portal areas or to central veins (attach the pathology report).

18. ☐ The HCV Infected Person has **undergone Compensable HCV Drug Therapy**. Provide the treatment dates pertaining to Compensable HCV Drug Therapy.

	Start Date DD/MM/YYYY	End Date DD/MM/YYYY
☐ Interferon therapy;	/ /	/ /
☐ Combination interferon/ribavirin therapy;	/ /	/ /
☐ Interferon combined with a drug other than ribavirin. Specify the other drug: _____	/ /	/ /
☐ Ribavirin combined with a drug other than interferon. Specify the other drug: _____	/ /	/ /

Is the Compensable HCV Drug Therapy ongoing?	Yes ☐ No ☐
Is the Compensable HCV Drug Therapy complete?	Yes ☐ No ☐
Please indicate the number of months of Compensable HCV Drug Therapy the HCV Infected Person has completed.	_____ months
Do you believe to a reasonable degree of medical certainty that the HCV Infected Person has cleared the Hepatitis C virus due to Compensable Drug Therapy?	Yes ☐ No ☐

19. ☐ The HCV Infected Person has **met or meets a protocol for Compensable HCV Drug Therapy** (treatment with interferon and/or ribavirin alone or in combination with each other or with other drugs) based on:

- ☐ being HCV RNA positive by PCR Test (attach the PCR Test); and
- ☐ having ALTs which were elevated 1.5 x normal for three or more months (attach the liver function test reports); and
- ☐ my opinion that the infection with HCV materially contributed to the elevated ALTs finding (attach a consultation or other report of a gastroenterologist, hepatologist or internist).
- ☐ I recommended Compensable HCV Drug Therapy treatment to the HCV Infected Person.
- ☐ I did not recommend Compensable HCV Drug Therapy treatment to the HCV Infected Person because: _____

SECTION E – PATIENT HISTORY

20.	How long have you known the HCV Infected Person?	
21.	How long have you treated the HCV Infected Person?	
22.	When was the last date you treated the HCV Infected Person for any condition?	/ /
23.	When was the last date you treated the HCV Infected Person for any condition related to the HCV?	/ /

SECTION F – HCV DISEASE VERIFICATION

24. Does/did the HCV Infected Person have a history of any of the following risk factors for the Hepatitis C virus other than a blood transfusion between **January 1, 1986 and July 1, 1990**? (Check all that apply.)

☐ Blood transfusions **prior to January 1, 1986**	☐ Non-prescription intravenous drug use	☐ Intra–nasal drug use
☐ Dialysis	☐ Tattoos	☐ None
☐ Transmission from an infected Spouse or Parent	☐ Body piercing (except ears)	☐ Other _____
☐ Prison incarceration	☐ Significant surgeries or trauma before January 1,1986 Enter date(s) at right	DD/MM/YYYY / / / /

HCV DISEASE VERIFICATION (CONTINUED)

The definition of Blood for the purpose of the **Transfused Plan** is as follows:
"Blood" means whole blood and the following Blood products: packed red cells, platelets, plasma (fresh frozen and banked), cryoprecipitate and white blood cells. **Blood does not include** Albumin 5%, Albumin 25%, Factor VIII, Porcine Factor VIII, Factor IX, Factor VII, Cytomegalovirus Immune Globulin, Hepatitis B Immune Globulin, Rh Immune Globulin, Varicella Zoster Immune Globulin, Immune Serum Globulin, (FEIBA) FEVIII Inhibitor Bypassing Activity, Autoplex (Activate Prothrombin Complex), Tetanus Immune Globulin, Intravenous Immune Globulin (IVIG) and Antithrombin III (ATIII).

25.	Based on the above definition of Blood, did the Primarily-Infected Person receive a Blood transfusion in the period January 1, 1986 to July 1,1990?	Yes ☐ No ☐
26.	Is there anything in the HCV Infected Person's medical history that indicates he or she was infected with **Hepatitis Non-A, Non-B** or the Hepatitis C virus prior to January 1, 1986?	Yes ☐ No ☐
	If yes, what in the HCV Infected Person's medical history indicates he or she may have been infected with Hepatitis Non-A, Non-B or the Hepatitis C virus prior to January 1, 1986? _____	
27.	Is there anything in the HCV Infected Person's medical history or clinical presentation that indicates he or she used non-prescription intravenous drugs at any time?	Yes ☐ No ☐
	If yes, what in the HCV Infected Person's medical history or clinical presentation indicates that he or she may have used non-prescription intravenous drugs?	
28.	A Secondarily-Infected Person claims to be **first** infected with HCV by his or her Parent or Spouse who is an HCV Infected Person. Is there anything in the Secondarily-Infected Person's medical history that indicates he or she was **first** infected with the Hepatitis C virus by any other means?	Yes ☐ No ☐
	If yes, what in the Secondarily-Infected Person's medical history indicates that he or she may have been **first** infected with the Hepatitis C virus by some means other than transmission from an infected Parent or Spouse?	
29.	Is/was the HCV Infected Person also infected with HIV? If yes, attach Lab Report.	Yes ☐ No ☐
30.	Are you aware of **any completed or requested** Traceback Procedures for the HCV Infected Person? If yes, provide documentation.	Yes ☐ No ☐
31.	If the HCV Infected Person has died, did his or her infection with the Hepatitis C virus materially contribute to his or her death?	Yes ☐ No ☐
	If yes, how did the HCV Infected Person's infection with HCV materially contribute to his or her death?	
	Attach the medical death certificate and autopsy report for the deceased HCV Infected Person.	

Go to Section H – Certification by Treating Physician on page 7.

COMPLETE SECTION G IF CLAIMING LOSS OF INCOME/LOSS OF SERVICES/LOSS OF SUPPORT

Note 1: The next Section, Section G, must be completed by the Treating Physician in the event that a claimant is eligible and intends to make a Claim for compensation for Loss of Income, Loss of Services in the Home or if the HCV Infected Person is deceased, compensation for Loss of Support payable to Approved Dependants of the HCV Infected Person.

Eligibility Summary

- All claimants who are approved at disease level 4, 5 or 6 who have suffered a loss of income/services/support.
- Claimants who are approved at disease level 3 and due to their HCV infection are unable to perform no more than 20% of the substantial duties of his or her employment/duties he or she would normally provide in his or her home.

Note 2: Section G may be completed at a later date if the claimant's eligibility or intention is unclear at the time of the initial application for compensation. If the claimant and/or the Physician opts to complete Section G at a later date, please go to Section H.

SECTION G – DISABILITY INFORMATION		
• If the HCV Infected Person has Disease Level 3, please complete questions 1 to 5. • If the HCV Infected Person has Disease Level 4, 5 or 6 please complete questions 6 to 11.		
DISEASE LEVEL 3 ONLY		
1.	Considering the information provided on the GEN 11 Form Activities of Employment and/or the GEN 12 Form Services in the Home, and any other relevant factors does the medical condition at Disease Level 3 cause the HCV Infected Person to be regularly unable to perform:	
	a) the substantial duties of his or her usual employment, occupation or profession such that he or she works no more than 20% of his or her usual work week.	☐ Yes ☐ No
	b) the substantial household duties that he or she would normally provide in his or her home such that they perform no more than 20% of the household services that he or she would normally provide.	☐ Yes ☐ No
2.	Please indicate the HCV Infected Person's symptoms which have caused the impairment resulting in the disability: _____ _____ _____	
3.	If Question 1a) and/or b) are checked, please indicate the date when the HCV Infected Person first met the criteria for disease Level 3.	DD/MM/YYYY / /
4.	Indicate the date when the HCV Infected Person first became disabled as defined in question 1a) and/or b).	DD/MM/YYYY / /
5.	If the HCV Infected Person was able to return to more than 20% of his or her usual employment or household duties, please indicate the date they would no longer be deemed disabled as defined in question 1.	DD/MM/YYYY / /
DISEASE LEVEL 4 OR 5 OR 6		
6.	Considering the information provided on the GEN 11 Form Activities of Employment and/or the GEN 12 Form Services in the Home, and any other relevant factors does the medical condition at Disease Level 4, 5 or 6 cause the HCV Infected Person to be regularly or temporarily unable to perform:	
	a) the duties of their employment, occupation or profession as a result of their HCV infection; or	☐ Yes ☐ No
	b) their household duties as a result of their HCV Infection.	☐ Yes ☐ No
7.	Considering the activities described on the GEN 11 Form Activities of Employment and/or the GEN 12 Form Services in the Home, and any other relevant factors please provide your opinion as to the percentage of disability presently suffered by the HCV Infected Person. The HCV Infected Person is _____ percent disabled as a result of the HCV infection. If the HCV Infected Person was temporarily disabled as a result of the HCV infection, the percentage of disability was_____ percent.	
8.	Please indicate the HCV Infected Person's symptoms which have caused the impairment resulting in the disability: _____ _____ _____	

SECTION G – DISABILITY INFORMATION – (CONTINUED)			
9.	Please indicate the date of the first diagnosis of Disease Level 4 or higher.		DD/MM/YYYY / /
10.	In cases of temporary disability due to HCV infection, please indicate when the HCV Infected Person first became disabled along with the date he/she ceased to be disabled.	Start date DD/MM/YYYY / /	End Date DD/MM/YYYY / /
11.	Indicate the date the HCV Infected Person first had any extent of disability as a result of an impairment caused by his or her HCV infection.	Start date DD/MM/YYYY / /	End Date DD/MM/YYY / /

SECTION H – CERTIFICATION BY TREATING PHYSICIAN

I certify that the information provided is true and correct to the best of my knowledge, information and belief.

_____ _____

Date Signed Treating Physician's Signature

THE ATTACHED IS EXHIBIT "H" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

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

Robert P Myers MD MSc[1], Alnoor Ramji MD[2], Marc Bilodeau MD[3], Stephen Wong MD MHSc[4], Jordan J Feld MD MPH[5]

RP Myers, A Ramji, M Bilodeau, S Wong, JJ Feld. An update on the management of chronic hepatitis C: Consensus guidelines from the Canadian Association for the Study of the Liver. Can J Gastroenterol 2012;26(6):359-375.

Chronic hepatitis C remains a significant medical and economic burden in Canada, affecting nearly 1% of the population. Since the last consensus conference on the management of chronic hepatitis C, major advances have warranted 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 several single nucleotide polymorphisms associated with an increased probability of spontaneous and treatment-induced viral clearance have been identified. In light of this new evidence, a consensus development conference was held in November 2011; the present document highlights the results of the presentations and discussions surrounding these issues. It 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 protease inhibitors (boceprevir and telaprevir), including those who have previously failed pegylated interferon and ribavirin therapy. In addition, recommendations are made regarding approaches to reducing the burden of hepatitis C in Canada.

Key Words: *Antiviral; Boceprevir; Guideline; Hepatitis C; Interferon; Peginterferon; Protease inhibitor; Ribavirin; Telaprevir; Therapy; Treatment*

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

L'hépatite C chronique demeure un fardeau médical et économique important au Canada, qui touche près de 1 % de la population. Depuis la dernière conférence consensuelle sur la prise en charge de l'hépatite C, des progrès importants ont justifié une analyse des démarches de prise en charge recommandées pour ces patients. Plus précisément, on a mis au point des antiviraux à action directe aux taux de clairance virologique considérablement plus élevés que ceux des thérapies standards et on a découvert plusieurs polymorphismes à nucléotide unique associés à une augmentation de la probabilité de clairance virale spontanée et induite par un traitement. À la lumière de ces nouvelles données probantes, une conférence consensuelle a eu lieu en novembre 2011. Le présent document fait ressortir les résultats des présentations et des discussions sur le sujet. Il traite de l'épidémiologie de l'hépatite C au Canada, des approches favorisées à l'égard des tests diagnostiques et des recommandations pour le traitement des patients atteints d'une infection chronique au moyen des inhibiteurs de la protéase approuvés depuis peu (bocéprévir et télaprévir), y compris les patients qui n'avaient pas répondu à un traitement à l'interféron pégylé et à la ribavirine. En outre, il contient des recommandations sur les démarches pour réduire le fardeau de l'hépatite C au Canada.

PREAMBLE

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 produced following a consensus conference of Canadian experts held in Toronto, Ontario, November 19 to 20, 2011. The meeting, which was organized by the Canadian Association for the Study of the Liver (CASL) with funding from the Canadian Liver Foundation, was open to all interested parties including health care professionals, patients, and representatives from government and the pharmaceutical industry. The information in the present guidelines represents a synthesis of the evidence presented at the meeting and available at the time of publication with supplementation by the expert opinion of the authors. Any recommendations should be considered preferred approaches to care of the HCV-infected patient as opposed to strict standards of care. 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 the American Association for the Study of Liver Diseases (3) (Table 1).

Since the most recent update of the CASL management guidelines for chronic hepatitis C in 2007 (4), two major advances have occurred: the development of direct-acting antiviral agents (DAAs) with dramatically improved rates of virological clearance compared with standard therapy (5-9); and the recognition of several single nucleotide polymorphisms (SNPs) associated with an increased probability of spontaneous and treatment-induced viral clearance (10-13). Presently, the impact of these advances is largely restricted to patients with HCV genotype 1. Therefore, the current consensus document was developed as an update to previous guidelines with a focus on the management of genotype 1-infected patients rather than an exhaustive review of hepatitis C. Where preferred management approaches for other patient populations (eg, with non-1 genotypes) have changed, the relevant recommendations have been updated.

INTRODUCTION

Chronic hepatitis C remains a significant medical and economic burden in Canada (14). Although no large-scale serological surveys have been conducted to define the exact prevalence of hepatitis C, modelling studies suggest that approximately 0.8% of Canadians – corresponding to nearly 245,000 individuals – were infected as of 2007

[1]*Liver Unit, Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta;* [2]*Department of Gastroenterology, University of British Columbia, Vancouver, British Columbia;* [3]*Liver Unit, Department of Medicine, University of Montreal, Montreal, Quebec;* [4]*Section of Hepatology, Department of Internal Medicine, University of Manitoba, Winnipeg, Manitoba;* [5]*Toronto Western Hospital Liver Centre, University of Toronto, Toronto, 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, email rpmyers@ucalgary.ca

Received for publication March 22, 2012. Accepted April 7, 2012

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

Adapted from references 1-3

(Table 2) (15). Provincial and territorial estimates of HCV prevalence suggest substantial regional variation, ranging from 0.13% in Newfoundland to 3.9% in the Yukon. In Canada, approximately 60% of HCV cases are among current or former injection drug users (IDUs), 20% are among infected immigrants and 11% have received contaminated blood products, including patients with hemophilia (Table 2). Of the nearly 8000 incident cases in Canada in 2007, approximately 80% are estimated to have occurred via sharing of injecting equipment among IDUs, and most of the remainder among immigrants from endemic countries. A significant number of the estimated cases in Canada remain undiagnosed, although the exact proportion is unclear (15). Modelling data suggest that the prevalence of hepatitis C has likely peaked in Canada, but the incidence of more advanced HCV-related sequelae (eg, decompensated liver disease, hepatocellular carcinoma [HCC] and liver transplantations) are expected to rise for at least another decade (Table 3 and Figure 1) (15).

Given the alarming estimates of future disease burden, more accurate information regarding the incidence and prevalence of hepatitis C and its sequelae are 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.

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 IDUs 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 elimination of the virus, which is termed a sustained virological response (SVR).

TABLE 2
Modelled hepatitis C virus (HCV) prevalence according to exposure category in Canada, 2007*

Risk group	Population	HCV prevalence rate, %	Prevalent cases, n	Proportion of Canadian cases, %
IDU, total	268,200	52	140,000	58
Current IDU	84,400	62	52,500	22
Previous IDU	183,800	48	87,500	36
Transfusion	3,325,700	0.8	25,900	11
Hemophilia	2200	40	900	0.4
Other	27,624,300	0.27	75,800	31
Total	31,220,500	0.8	243,000	100

**Numbers rounded to the nearest 100. IDU Intravenous drug user. Data adapted from reference 15*

SVR is defined as undetectable serum HCV RNA at least 24 weeks following the end of treatment (Table 4) (16). Recent data suggest that earlier assessment of serum HCV RNA at 12 weeks after treatment is sufficient to define this outcome (17). Once achieved, an SVR is considered to be a cure of HCV infection because late relapses (which may actually represent reinfections) are rare (18,19). Additional benefits of SVR include improvements in quality of life (20,21), extrahepatic manifestations of HCV (eg, cryoglobulinemic vasculitis) (22), liver histology (23,24), and liver-related morbidity and mortality (25-27).

The landscape of antiviral treatment for hepatitis C is changing rapidly (28). Until recently, the standard therapy was the combination of peginterferon-alpha (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 (4). Dual therapy achieves SVR rates of 40% to 50% in patients with genotype 1, and approximately 80% in those with genotypes 2 and 3. Although a significant advance from previously available treatments, PEG-IFN and RBV therapy is costly, associated with numerous adverse events and has only been used in a minority of infected individuals (29,30). Moreover, the majority of patients in Canada have HCV genotype 1 and have a lower likelihood of achieving viral eradication with dual therapy. Therefore, the recent emergence of DAAs, which offer a substantial improvement in SVR rates and the option of abbreviated therapy for many genotype-1-infected patients, represents a major advance in the field.

The treatment of hepatitis C is complex and time-consuming. Anti-HCV therapies require multiple modes of administration, can have numerous side effects, and require careful monitoring of symptoms and laboratory tests. Treatment complexity is further exacerbated by comorbid conditions that are more prevalent among HCV-infected patients, including mental health disorders (eg, depression) and addictions (eg, to alcohol and drugs). Therefore, the optimal management of hepatitis C requires a multidisciplinary approach that includes 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 hepatitis C, leading in some cases to prolonged wait times for patients before being adequately evaluated and treated. Moreover, public funding for treatment nurses – who are a vital component of the management team – is not universally available. To achieve a meaningful reduction in the future burden of this disease, it will be vital to expand treatment capacity via additional training and funding of experienced personnel and enhanced access to publicly funded antiviral therapies (31).

Recommendations:

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).

TABLE 3
Modelled burden of hepatitis C virus (HCV) and sequelae according to five-year intervals in Canada, 1977 to 2027*

Year	HCV		Cirrhosis	Decompensated liver disease	Hepatocellular carcinoma	Liver transplants	Liver-related deaths
	Prevalence	Incidence					
1977	179,224	24,233	3611	743	69	99	77
1982	232,945	24,834	5605	1252	109	181	125
1987	264,095	18,497	7934	1940	158	304	189
1992	263,878	9486	10,477	2799	215	474	266
1997	254,165	8058	12,690	3748	266	688	346
2002	246,682	7899	14,421	4666	305	933	419
2007	242,521	7945	15,814	5495	338	1187	483
2012	239,134	8135	16,755	6186	360	1430	534
2017	236,343	8269	17,333	6721	373	1649	572
2022	232,684	8166	17,592	7101	378	1833	599
2027	227,371	7959	17,570	7333	379	1976	613

*Data presented as n. *Estimates are not mutually exclusive. Data adapted from reference 15*

INDICATIONS AND CONTRAINDICATIONS TO ANTIVIRAL TREATMENT

All patients with chronic hepatitis C who have compensated liver disease, are willing to undergo therapy and have no contraindications, should be considered candidates for antiviral treatment. The decision regarding 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 patient's anticipated tolerability of treatment and the life expectancy of the patient (eg, considering comorbidities). Women of childbearing potential may elect to undergo antiviral therapy before having children to reduce the risk of vertical transmission. The prospect of novel therapies with expected benefits over currently available treatments should also be considered. There is no absolute fibrosis threshold that should be used to preclude antiviral therapy; however, prompt initiation of treatment should be considered in patients with advanced liver fibrosis (F3 or F4 according to the METAVIR classification [bridging fibrosis or cirrhosis]) (32). These patients are at the highest risk of HCV-related complications including liver failure and HCC. Treatment of patients with lesser degrees of fibrosis (F0 to F2) should also be considered because progression to more advanced stages is associated with a reduced likelihood of SVR (5,6,33) but needs to be discussed on an individualized basis. Patients with extrahepatic manifestations of chronic hepatitis C 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 (22).

There are very few absolute contraindications to treatment with PEG-IFN and RBV-based therapy. As postmarketing experience with these medications has grown, many conditions previously regarded as absolute contraindications are now considered relative, and some may be present only temporarily (Table 5) (4). In most cases, treatment of these patients requires considerable expertise and, therefore, patients with relative contraindications should be treated in expert centres.

In some regions within Canada, public reimbursement for therapy is restricted to patients with elevated serum alanine aminotransferase (ALT) concentrations. Normal ALT is not a contraindication to treatment. These patients, which comprise approximately one-third of chronically infected individuals, respond as well to therapy as patients with elevated ALT levels (34). Moreover, approximately one-quarter of patients with persistently normal ALT levels have moderate to severe liver disease on biopsy (35).

Finally, patients who are incarcerated – a population with a high prevalence of HCV infection – should be considered for antiviral therapy as per nonincarcerated individuals. In appropriately selected

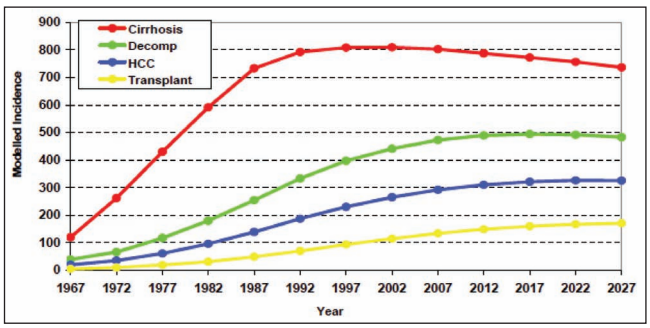


Figure 1) *Modelled incidence of hepatitis C-related sequelae according to five-year intervals in Canada, 1967 to 2027. Estimates are not mutually exclusive. Reproduced with permission from reference 15. Decomp Decompensated liver disease; HCC Hepatocellular carcinoma*

TABLE 4
Definitions of virological response to pegylated interferon (PEG-IFN) and ribavirin (RBV)-based therapy

Virological response	Definition
Rapid virological response	Undetectable HCV RNA at week 4 of therapy
Extended rapid virological response	Undetectable HCV RNA at weeks 4 and 12 of therapy in patients treated with telaprevir-based triple therapy
Early virological response	≥2 $\log_{10}$ decrease in HCV RNA at week 12 compared with baseline
End-of-treatment virological response	Undetectable HCV RNA at the end of treatment
Sustained virological response	Undetectable HCV RNA at least 24 weeks following the end of treatment
Null response	<2 $\log_{10}$ decrease in HCV RNA at week 12 compared with baseline in patients treated with PEG-IFN and RBV
Partial response	≥2 $\log_{10}$ decrease in HCV RNA but still detectable at week 12 in patients treated with PEG-IFN and RBV
Virological breakthrough	Reappearance of HCV RNA at any time during treatment after HCV RNA negativity has been achieved
Relapse	Reappearance of HCV RNA following treatment discontinuation after an end of treatment virological response has been achieved

HCV Hepatitis C virus

TABLE 5
Contraindications to treatment with pegylated interferon and ribavirin

Absolute contraindication	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
	Renal failure (including dialysis)
Patient characteristics that are no longer considered to be contraindications	Normal alanine aminotransferase level
	Injection drug use
	Stable methadone maintenance
	Neutropenia, anemia or thrombocytopenia
	Controlled seizure disorder
	Older than 65 years of age
	Alcohol use

Table adapted with permission from reference 4

inmates, the ability to achieve an SVR with IFN-based therapy is similar to patients treated in the community (36,37). Treatment should be reserved for inmates deemed to be at low risk for HCV reinfection.

Recommendations:

4. All patients with chronic HCV infection should be considered candidates for antiviral therapy, particularly those with evidence of liver fibrosis (Class 1, Level A).
5. Patients with extrahepatic manifestations of HCV infection should be considered for antiviral therapy (Class 1, Level B).
6. Persistently normal ALT does not exclude significant liver disease nor preclude the need for antiviral therapy (Class 1, Level A).

PRETREATMENT ASSESSMENT

Routine assessment

The routine assessment of patients with chronic hepatitis C should include risk factors for viral acquisition (eg, IDU, 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), presence of cofactors that may accelerate disease progression (eg, alcohol abuse, obesity, coinfections) and potential contraindications to IFN-based therapy (Table 5). Necessary laboratory testing includes virological tests to confirm and characterize HCV infection, liver biochemistry, abdominal ultrasound, and tests to rule out coinfections, direct vaccination and identify contraindications to treatment. In patients with abnormal liver biochemistry, serological tests to exclude coexisting liver diseases should be considered (Table 6).

Virological testing

Approximately one-quarter of patients who have been infected with HCV have cleared the virus spontaneously (38). Therefore, chronic HCV infection must be confirmed in all anti-HCV-positive individuals using a sensitive HCV RNA test. When contemplating therapy, HCV RNA should also be quantified to serve as a baseline for on-treatment monitoring of viral kinetics. HCV RNA detection and quantification using real-time polymerase chain reaction assays is standard due to their sensitivity, specificity, accuracy and broad dynamic range. Assays should be calibrated to the WHO international standard and results should be expressed in IU/mL. Quantitative assays with a lower limit of detection of approximately 10 IU/mL to 15 IU/mL are recommended. To facilitate management decisions, HCV RNA test results should be available within a timely fashion (seven days or less). The rapid identification of failing antiviral therapy will reduce patient exposure to costly and potentially toxic therapies, and likely

TABLE 6
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	Directs choice and duration of therapy
Assessment of liver disease	Complete blood count, ALT, AST, GGT, Alkaline phosphatase	Thrombocytopenia may indicate cirrhosis and portal hypertension. Platelets needed for APRI calculation. Normal value does not preclude significant fibrosis. AST needed for calculation of APRI
	Bilirubin, INR (or PT), Albumin	Elevated bilirubin or INR, or hypoalbuminemia may indicate significant liver dysfunction
	Creatinine, abdominal ultrasound	May suggest cirrhosis, in which case, serves as a baseline for HCC surveillance
Viral coinfections	Immunoglobulin G anti-HAV	If negative, vaccinate against hepatitis A virus (HAV)
	HBsAg	Exclude hepatitis B coinfection.
	anti-HBs	If negative (and HBsAg-negative), vaccinate against hepatitis B
	anti-HIV	Exclude HIV coinfection
Exclude other causes of liver disease†	Alpha-1-antitrypsin	Alpha-1-antitrypsin deficiency
	Ceruloplasmin	Wilson disease
	Ferritin, serum iron, total iron-binding capacity	Iron overload
	Antinuclear antibody, smooth muscle antibody	Autoimmune hepatitis (AIH)
	Antimitochrondrial antibody	Primary biliary cirrhosis (PBC)
	Immunoglobulin G	Often elevated in AIH and cirrhosis of any cause
	Immunoglobulin A	Often elevated in fatty liver and alcoholic liver disease
	Immunoglobulin M	Often elevated in PBC
Contraindications to treatment	Serum or urine β-HCG	Exclude pregnancy in women of reproductive age
	Electrocardiogram	If >50 years or history of cardiac disease
	Thyroid-stimulating hormone	Exclude thyroid disease, which may be exacerbated by IFN
	Fundoscopy	Exclude retinopathy in patients >50 years or with hypertension or diabetes mellitus

**Confirmed anti-HCV antibody positive; †Suggested tests only. Tailor testing to individual case. Anti-HBs Hepatitis B surface antibody; ALT Alanine aminotransferase; AST Aspartate aminotransferase; APRI AST/platelet ratio index; β-HCG Beta-human chorionic gonadotropin; GGT Gamma-glutamyltransferase; HBsAg Hepatitis B surface antigen; HCC Hepatocellular carcinoma; IFN Interferon; INR International normalized ratio; PT Prothrombin time*

limit the development of antiviral-resistant variants (see below regarding discussion of futility rules).

The HCV genotype should also be assessed because it has important implications for the decision to initiate treatment, the choice of treatment, the dosage of RBV and the duration of therapy. With PEG-IFN and RBV treatment, knowledge of only the main genotype (1 to 6) is necessary. However, with the advent of the first-generation DAAs (telaprevir and boceprevir), knowledge of the subtype may be useful due to differing genetic barriers to resistance between HCV subtypes 1a and 1b (39,40).

Recommendations:

7. HCV RNA and genotype testing are essential to the management of patients with chronic hepatitis C (Class 1, Level C).
8. HCV RNA testing should be performed using a sensitive quantitative assay (lower limit of detection of 10 IU/mL to 15 IU/mL or less) 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 C).

Assessment of liver disease severity

Assessment of the severity of hepatic fibrosis is vital for determining the necessity of antiviral treatment and determining the prognosis of patients with chronic hepatitis C. Identification of patients with cirrhosis is particularly important due to their increased risk of hepatic complications (eg, HCC and end-stage liver disease), reduced responsiveness to antiviral treatment, and their need 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), liver biopsy has traditionally been the reference method for staging liver fibrosis, determining the severity of other histological lesions (eg, necroinflammation, steatosis) and ruling out coexistent liver diseases (eg, iron overload). Various scoring systems have been validated for use in chronic hepatitis C and demonstrated sufficient reproducibility and interobserver variability to justify clinical use. The most widely used include the METAVIR, Scheuer, Ishak index and Knodell's Hepatic Activity Index classifications (41). However, liver biopsy has several limitations, most notably its invasiveness and the potential for serious complications including hemorrhage (approximately one in 1000) and death (approximately one in 10,000) (42,43). Other limitations include sampling error and variability in pathological interpretation (both of which may limit the accuracy of its findings), high cost 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 including serum markers, transient elastography (TE) and other imaging-based tools (44).

Serum marker panels that are available to stage fibrosis in patients with chronic hepatitis C can be categorized into three broad categories:

1. Panels based on routinely available biochemical and hematological parameters including ALT, aspartate aminotransferase (AST) and platelets (eg, the AST/ALT ratio [45], the AST/platelet ratio index [46] and Forns' index [47]);
2. Panels that include indirect markers of liver fibrosis such as alpha-2-macroglobulin and haptoglobin (eg, FibroTest [48], Hepascore [49] and FibroMeter [50]); and
3. Panels that include direct markers of fibrosis such as hyaluronic acid and tissue inhibitor of matrix metalloproteinase-1 (eg, FibroSpect II [51] and Enhanced Liver Fibrosis test [52]).

TE (FibroScan, Echosens, France) is an ultrasound-based method that measures liver stiffness as a surrogate of liver fibrosis. Numerous studies have validated this tool for staging of fibrosis in patients with chronic hepatitis C and other liver conditions (53-55). To obtain accurate TE results, it is important to consider factors that may influence liver stiffness such as nonfibrotic histological lesions (eg, inflammation, vascular congestion and cholestasis) and obesity (55). In obese patients (body mass index [BMI] ≥30 kg/m^2), it is advisable to use a specially designed probe (the FibroScan XL probe), which reduces the likelihood of TE failure compared with the standard M probe (56). Moreover, TE results must be interpreted cautiously when few valid measurements are obtained (ie, <10 valid shots or success rate <60%) or when the results are highly variable (ie, interquartile range of measurements over the median value >30%) (56-58).

Several additional imaging-based methods have been developed and hold promise for the noninvasive staging of liver fibrosis. These include acoustic radiation force impulse imaging, magnetic resonance (MR) elastography, diffusion-weighted MR imaging and MR spectroscopy (59,60). Although promising, the widespread adoption of these methods requires additional validation.

Although not universally available, a wealth of literature has now confirmed that serum biomarker panels and TE can be used instead of liver biopsy to stage HCV-related liver fibrosis with acceptable levels of accuracy and reproducibility. In general, these tests are highly accurate for diagnosing cirrhosis and have acceptable, but lower, performance for moderate to severe fibrosis (≥F2). The identification of mild fibrosis (F1) and the differentiation between individual stages is poor; these limitations also apply to liver biopsy. The combination of two serum marker panels or TE with a serum marker panel can improve accuracy, although the added cost of this approach requires consideration (61,62). Emerging data have also demonstrated a correlation between these tests and clinical outcomes of HCV (63,64) as well as responsiveness to successful 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. All patients with HCV should undergo an assessment for the severity of liver fibrosis. Acceptable methods include liver biopsy, elastography (eg, FibroScan) and serum biomarker panels (eg, AST/platelet ratio index, FibroTest, FibroMeter), either alone or in combination (Class 2a, Level B).
10. Alternatively, cirrhosis can be 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 SNPs near the interleukin 28B (IL28B) gene on chromosome 19 that are strongly associated with both spontaneous and PEG-IFN- and RBV treatment-induced HCV clearance (10-13). Patients with the favourable CC genotype at rs12979860 have a more than twofold likelihood of spontaneous HCV clearance compared with heterozygotes (CT) and TT homozygotes (10). The CC genotype is also associated with a higher rate of SVR to PEG-IFN and RBV therapy. Caucasian patients with the CC IL28B genotype and HCV genotype 1 have an approximately 80% chance of SVR compared with just 40% among those with non-CC genotypes (11). There is marked ethnic variation in the prevalence of the IL28B genotypes. The CC genotype is highly prevalent in Asians, but relatively uncommon in Africans; Caucasians and Hispanics have an intermediate prevalence (11). Within ethnicities, the CC genotype is 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 (11). It is estimated that inter-racial differences in the prevalence of the IL28B genotypes account for approximately 50% of the ethnic variation in response rates to this therapy (11). Similar associations have been reported for the rs8099917 SNP, in which the favourable allele is coded with a T and the unfavourable allele with a G (13).

In patients with HCV genotype 1, the IL28B genotype is the strongest pretreatment predictor of response to PEG-IFN and RBV therapy (67). However, although patients with the favourable IL28B

TABLE 7
Futility rules in treatment-naive and previous treatment failure patients treated with boceprevir- or telaprevir-based triple therapy

Boceprevir	HCV RNA result*	Action
Week 12	≥100 IU/mL	Stop all therapy
Week 24	Detectable	Stop all therapy
Telaprevir	**HCV RNA result***	**Action**
Week 4	>1000 IU/mL	Stop all therapy
Week 12	>1000 IU/mL	Stop all therapy
Week 24	Detectable	Stop all therapy

**Hepatitis C virus (HCV) RNA should be quantified using an assay with a lower limit of detection of no greater than 10 IU/mL to 15 IU/mL*

CC genotype are likely to respond (approximately 80%), many patients with unfavourable genotypes will also respond (approximately 40%) (11). As such, the negative predictive value of the unfavourable genotypes is insufficient to preclude dual therapy in the individual patient. The impact of the IL28B genotype on treatment success is lower when treatment includes DAAs. Previously untreated patients with the favourable CC genotype are very likely to respond to combination therapy including DAAs, and the vast majority will qualify for shortened treatment. DAAs lead to a greater relative increase in SVR in non-CC patients (68,69). In treatment-experienced individuals, the IL28B genotype is of limited value (70); the outcome of DAA therapy in this population is largely dictated by the previous response to PEG-IFN and RBV, with prior relapsers showing two- to threefold higher SVR rates than null responders (8). The prior response is partly reflective of a patient's IL28B genotype and, hence, few null responders have the CC genotype. However, after stratification according to previous treatment response, there are no differences in rates of SVR to DAA-based therapy across IL28B genotypes (70). Similarly, on-treatment responses – to either dual or triple therapy – are better predictors of outcome than the IL28B genotype (67,69,71). Although non-CC patients achieve a rapid virological response (RVR; Table 4) to PEG-IFN and RBV less frequently than patients with the CC genotype, for those who do achieve an RVR, the rate of SVR is greater than that of CC patients who do not achieve RVR (71).

The mechanisms underlying the association of the IL28B genotype with antiviral treatment response are unknown. The SNPs lie in close proximity to – but not within – the IL28B gene, which codes for IL28B, also known as interferon (IFN) lambda. IFN-lambda is a type III IFN that signals similarly to type I IFNs (alpha or beta) but binds to a different receptor with a more limited tissue distribution (72). Because the IL28B genotype affects the response to IFN, it is most relevant in the least IFN-responsive HCV genotypes. Specifically, whereas the IL28B genotype is associated with SVR rates in genotypes 1 and 4 (73,74), its role in genotypes 2 and 3 is questionable (75,76).

In summary, IL28B genotyping may provide information regarding the likelihood of treatment response, but should not be used to determine the need or eligibility for therapy, or to determine the type of therapy used. Although patients with the favourable CC genotype are more likely to achieve an RVR to PEG-IFN and RBV, and may not all benefit from the addition of a DAA due to their high likelihood of SVR with dual therapy alone, there are insufficient data to support altering treatment paradigms based on the IL28B genotype.

Recommendations:

11. The IL28B genotype may provide some information regarding the likelihood of SVR and the probability of qualifying for shortened treatment duration in previously untreated patients with HCV genotype 1 (Class 1, Level A).
12. The role of IL28B genotyping is limited in treatment-experienced patients and those with HCV genotypes other than 1 and 4 (Class 3, Level A).
13. A nonfavourable IL28B genotype does not preclude antiviral therapy (Class 2b, Level C).

DAA AGENTS

Multiple steps in the HCV life cycle represent attractive targets for novel pharmacological therapies. Particularly promising agents target the nonstructural (NS) 3/4A (NS3/4A) serine protease, the NS5B RNA-dependent RNA polymerase and the NS5A protein (28). Several host-targeted agents, including the cyclophilin inhibitors, are also in development. Currently, the only DAAs to receive approval from Health Canada and the United States Food and Drug Administration are the NS3/4A protease inhibitors (PIs) boceprevir and telaprevir. When combined with PEG-IFN and RBV, these drugs lead to markedly improved SVR rates and permit shortened therapy in a significant proportion of patients with HCV genotype 1 (5-9). Based on currently available data, these agents should not be used in patients with non-1 genotypes. Importantly, the PIs must be used in combination with both PEG-IFN and RBV. If either of these medications is discontinued, the PI must also be discontinued.

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPE 1

Boceprevir

Boceprevir was formally evaluated in the Serine Protease Inhibitor Therapy 2 (SPRINT-2) trial, a phase 3 study that compared three regimens in two cohorts (nonblack and black) of treatment-naive patients with HCV genotype 1 infection (77). All patients were first treated with PEG-IFN-alfa-2b (1.5 µg/kg/week) and RBV (600 mg/day to 1400 mg/day based on body weight) for a four-week lead-in period. After the lead-in period, the control arm received an additional 44 weeks of PEG-IFN and RBV dual therapy. In the 'response-guided therapy' (RGT) arm, patients received PEG-IFN, RBV and boceprevir for 24 weeks after the lead-in period. In patients with undetectable (<10 IU/mL) HCV RNA from weeks 8 through 24, treatment was terminated, but if HCV RNA was detectable at any point from week 8 up to but not including week 24, an additional 20 weeks of PEG-IFN and RBV was administered. In the third arm, patients in the 'fixed-duration therapy' (FIXED) group received boceprevir plus PEG-IFN and RBV for 44 weeks after the lead-in period. The dosage of boceprevir was 800 mg three times daily (taken orally every 7 h to 9 h with food). All patients with detectable HCV RNA at week 24 were discontinued from treatment due to futility. A post hoc analysis has also identified that treatment continuation is futile in patients with HCV RNA ≥100 IU/mL at week 12 (Table 7) (78).

Overall, the rates of SVR in the SPRINT-2 trial were higher in boceprevir-treated patients (63% in the RGT arm and 66% in the FIXED arm) compared with those who received dual therapy (38%) (5). SVR rates in the nonblack patients were similar (RGT 67%; FIXED 68%; control 40%), whereas lower responses were observed among black patients (RGT 42%; FIXED 53%; control 23%). Treatment with a boceprevir-containing regimen was superior to dual therapy for most pretreatment factors including age, sex, race, viral load, body weight and BMI.

Forty-four per cent of boceprevir-treated patients had undetectable HCV RNA at treatment weeks 8 through 24 (early responders), compared with 12% of control patients, and would be eligible to shorten treatment to 28 weeks according to an RGT approach. In these patients, the SVR rates were 96%, 96% and 93% in the RGT, FIXED, and control groups, respectively (5). Overall, the SVR rates in the RGT and FIXED boceprevir arms were similar, supporting the use of RGT in most patients. In a subgroup analysis of the SPRINT-2 study, the SVR rate was superior in patients with cirrhosis (F4) in the FIXED arm (42%) compared with the RGT arm (31%). Although this difference was not statistically significant, the small number of cirrhotic patients in this analysis (n=40) supports a conservative approach in this difficult-to-cure subgroup. Therefore, in patients with cirrhosis, a

TABLE 8
Duration of therapy using response-guided therapy guidelines in patients treated with boceprevir- or telaprevir-based triple therapy

	HCV RNA result*		
Boceprevir†	**Week 8**	**Week 24**	**Action**
Previously untreated patients	Undetectable	Undetectable	Stop boceprevir, PEG-IFN and RBV at treatment week 28. Treatment is completed.
	Detectable	Undetectable	Continue boceprevir, PEG-IFN and RBV until treatment week 28 and then administer PEG-IFN and RBV until week 48.
Previous treatment failures (relapsers and partial responders)	Undetectable	Undetectable	Stop boceprevir, PEG-IFN and RBV at treatment week 36. Treatment is completed.
	Detectable	Undetectable	Continue boceprevir, PEG-IFN and RBV until treatment week 36 and then administer PEG-IFN and RBV until week 48.
	HCV RNA result		
Telaprevir‡	**Week 4**	**Week 12**	**Action**
Previously untreated patients and relapsers	Undetectable	Undetectable	Stop telaprevir at treatment week 12 and then continue PEG-IFN and RBV until week 24.
	Detectable§	Undetectable or detectable§	Stop telaprevir at treatment week 12 and then continue PEG-IFN and RBV until week 48.

**Hepatitis C virus (HCV) RNA should be quantified using an assay with a lower limit of detection of no greater than 10 IU/mL to 15 IU/mL; †Response-guided therapy to boceprevir is not recommended for patients with cirrhosis (F4), null responders to previous pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy, or patients with a less than 1 $\log_{10}$ decline in HCV RNA at treatment week 4 compared with baseline; ‡Response-guided therapy to telaprevir is not recommended for patients with cirrhosis (F4) or previous partial or null responders to PEG-IFN and RBV therapy; §Detectable, but ≤1000 IU/mL. Higher values necessitate discontinuation of all therapy (see Table 7).*

fixed duration of treatment consisting of 44 weeks of triple therapy after the lead-in phase is recommended. Similarly, patients who have less than a 1 $\log_{10}$ decline in viral load from baseline to treatment week 4 during the lead-in period should receive an additional 44 weeks of triple therapy. While SVR rates among IFN-responsive patients in the SPRINT-2 trial were similar in the RGT and FIXED arms (approximately 80%), poorly responsive patients had a numerically higher SVR rate in the FIXED compared with the RGT arm (38% versus 28%) (5).

Recommendations (Figure 2):

14. Patients should receive a four-week lead-in period of PEG-IFN and RBV before the initiation of boceprevir (Class 2b, Level A).
15. Boceprevir is given at a dosage of 800 mg (4 × 200 mg capsules) every 8 h with food (Class 1, Level A).
16. RGT (Table 8): In noncirrhotic patients with undetectable HCV RNA at treatment weeks 8 through 24 (ie, four and 20 weeks after starting boceprevir), all therapy may be discontinued at week 28 (Class 1, Level B).
17. In patients with detectable HCV RNA at treatment week 8, triple therapy should be continued until week 28. At this point, boceprevir should be discontinued and PEG-IFN and RBV should be continued for an additional 20 weeks (Class 1, Level B).
18. Patients with cirrhosis and those with <1 $\log_{10}$ decline in HCV RNA after the four-week lead-in period should receive triple therapy for 44 weeks following the lead-in period (Class 2a, Level B).
19. Futility rules (Table 7): All treatment should be discontinued in patients with HCV RNA ≥100 IU/mL at treatment week 12 or detectable HCV RNA at week 24 (Class 2a, Level B).

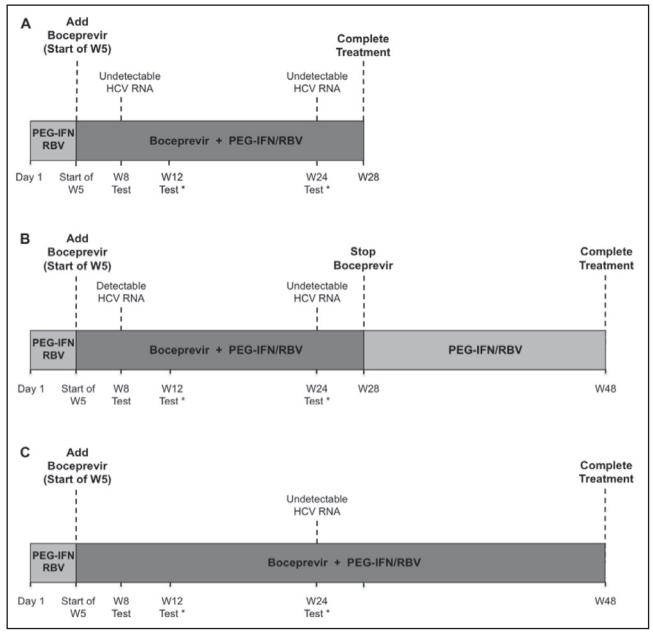


Figure 2) *Algorithm for the management of treatment-naive patients with hepatitis C virus (HCV) genotype 1 treated with pegylated interferon (PEG-IFN), ribavirin (RBV) and boceprevir.* **A** *Early responders (defined as HCV RNA-negative at weeks 8 through 24) are eligible for response-guided therapy (RGT) (28 weeks total treatment).* **B** *Late responders defined as HCV RNA-positive at week 8 should not receive RGT (ie, treat for 48 weeks total).* **C** *Patients with cirrhosis (F4) or <1 $\log_{10}$ decrease in HCV RNA from baseline to week 4 after the lead-in phase should receive 48 weeks of treatment (ie, not RGT). *Indicates discontinuation of all treatment due to futility in patients with HCV RNA ≥100 IU/mL at treatment week 12 or detectable HCV RNA at week 24*

Telaprevir

Telaprevir has been evaluated in two phase 3 trials that included treatment-naive patients with HCV genotype 1 infection (6,7). In the A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir (ADVANCE) trial, patients were randomized to one of three treatment groups. The control arm received PEG-IFN-alpha-2a (180 µg/week) and RBV (1000 mg/day to 1200 mg/day based on body weight) for 48 weeks (PR48), while two telaprevir-treated groups also received telaprevir for the first 8 (T8PR) or 12 weeks (T12PR) in addition to PEG-IFN and RBV (6). Telaprevir was administered at a dose of 750 mg every 8 h with high fat content food (approximately 20 g). Patients in the T8PR and T12PR groups who achieved an extended RVR (eRVR), defined as undetectable HCV RNA (<10 IU/mL) at weeks 4 and 12 (Table 4), stopped all therapy at week 24 according to an RGT approach. The rates of SVR were higher in both telaprevir-treated arms (T12PR, 75% and T8PR, 69%) than in the PR48 arm (44%) (6). Although the study was underpowered to compare the T12PR and T8PR groups, trends toward improved efficacy

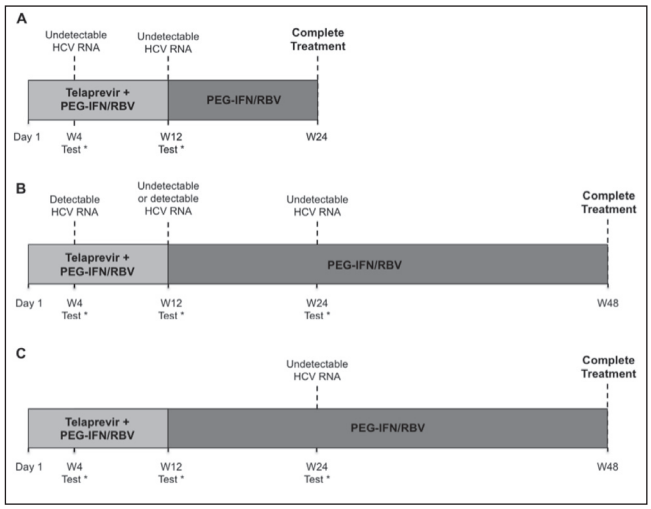


Figure 3) *Algorithm for the management of treatment-naive patients with hepatitis C virus (HCV) genotype 1 treated with pegylated interferon (PEG-IFN), ribavirin (RBV) and telaprevir.* **A** *Patients with an extended rapid virological response (HCV RNA-negative at weeks 4 and 12) are eligible for response-guided therapy (RGT) (24 weeks total treatment).* **B** *Patients who do not achieve an extended rapid virological response should not receive RGT (ie, treat for 48 weeks total).* **C** *Patients with cirrhosis should receive 48 weeks of treatment (ie, not RGT). *Indicates discontinuation of all treatment due to futility in patients with HCV RNA >1000 IU/mL at treatment weeks 4 or 12, or detectable HCV RNA at week 24*

in some difficult-to-cure subgroups (eg, genotype 1a, high viral load and advanced fibrosis) and reduced emergence of antiviral-resistant variants were noted in the T12PR arm. Although 12-week dosing of telaprevir is likely preferable, the data suggest that if a patient must discontinue telaprevir prematurely due to adverse effects, high rates of SVR remain possible.

In addition to higher SVR rates, many patients were able to shorten treatment with the addition of telaprevir to PEG-IFN and RBV. Using an RGT approach, 57% to 58% of telaprevir-treated patients had an eRVR (compared with only 8% of PR patients) and were able to discontinue therapy at 24 weeks. The SVR rate for those who achieved eRVR was 89% in the T12PR arm and 83% in the T8PR group (versus 97% in the PR group), indicating that eRVR is a very robust predictor of SVR (6). To validate RGT as an appropriate strategy, the Illustrating the Effects of Combination Therapy with Telaprevir (ILLUMINATE) trial randomly assigned patients achieving an eRVR after 12 weeks of telaprevir-based triple therapy to 24 or 48 weeks of total treatment (7). Of the 540 patients included, 65% achieved an eRVR and were randomized. The SVR rates in patients with eRVR treated for 24 and 48 weeks were 92% and 88%, respectively, indicating that treatment can be shortened in patients who achieve an eRVR without a loss in the rate of SVR (7). However, RGT may not be the preferred strategy in patients with cirrhosis. In the ILLUMINATE trial, 61 patients (11%) had cirrhosis at baseline and 30 patients (49%) achieved an eRVR. Of these 30 patients, only 12 of the 18 (67%) randomly assigned to stop therapy at 24 weeks achieved SVR, compared with 11 of the 12 (92%) who were treated for a full 48 weeks (7). Based on these data, it is recommended that all patients with cirrhosis receive 12 weeks of telaprevir-based triple therapy followed by an additional 36 weeks of PEG-IFN and RBV. Other predictors of poor IFN responsiveness, such as high viral load and black race, had smaller effects on treatment outcome and, hence, RGT is still recommended for these subgroups.

Patients treated with telaprevir who have HCV RNA levels >1000 IU/mL at weeks 4 or 12 should stop all treatment because no patients meeting these futility rules in the phase 3 trials achieved SVR (6-8,79,80). Notably, in almost all patients with viral levels exceeding 1000 IU/mL at weeks 4 or 12, the viral titre is rising rather than falling due the presence of telaprevir resistance. Continuation of therapy in the presence of resistance may promote compensatory mutations in the resistant variants that will improve their replicative fitness over time (81). In addition, continuation of futile therapy adds to cost and the potential for adverse effects.

Recommendations (Figure 3):

20. Telaprevir should be started simultaneously with PEG-IFN and RBV and given for the initial 12 weeks of therapy (Class 1, Level A).
21. Telaprevir is given at a dosage of 750 mg (2 × 375 mg tablets) every 8 h with high-fat food (Class 1, Level A).
22. RGT (Table 8): In noncirrhotic patients with undetectable HCV RNA at treatment weeks 4 and 12 (eRVR), telaprevir should be discontinued at week 12 and PEG-IFN and RBV should be continued for an additional 12 weeks (Class 1, Level A).
23. In patients with detectable HCV RNA at weeks 4 or 12, telaprevir should be stopped at week 12 and PEG-IFN and RBV should be continued for an additional 36 weeks (Class 1, Level A).
24. Patients with cirrhosis should receive 12 weeks of triple therapy followed by an additional 36 weeks of PEG-IFN and RBV (Class 2a, Level B).
25. Futility rules (Table 7): All treatment should be discontinued in patients with HCV RNA >1000 IU/mL at treatment weeks 4 or 12, or detectable HCV RNA at week 24 (Class 1, Level A).

Dual therapy in patients with RVR to PEG-IFN and RBV

Genotype 1-infected patients with an RVR, defined as undetectable HCV RNA after 4 weeks of PEG-IFN and RBV therapy (Table 4), may not benefit from the addition of a PI. In the SPRINT-2 (5), ADVANCE (6) and Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) trials (33), 8% to 12% of treatment-naive patients who received PEG-IFN and RBV dual therapy achieved an RVR. The majority of these patients had the favourable IL28B genotype (CC). In patients who achieved RVR in these trials, dual therapy for 48 weeks led to an SVR in 86% to 97% of patients, similar to rates achieved with PI-based triple therapy (RGT and fixed duration). In the small subset of patients with RVR and low baseline viral load (<400,000 IU/mL), dual therapy for only 24 weeks yielded SVR rates comparable with 48 weeks of PEG-IFN and RBV treatment (82). The obvious benefits of avoiding a DAA in this patient subgroup include reduced exposure to PI-related adverse events, lower cost and the avoidance of emergent antiviral resistant variants in the small proportion of patients who subsequently fail this treatment. On the other hand, there are several hurdles to using this strategy. Notably, a lead-in strategy was used only in the phase 3 trials of boceprevir (not telaprevir) for treatment-naive patients. Although a lead-in approach could be adopted before use of either PI, the decision to add a PI in patients who do not achieve an RVR would require rapid access to HCV RNA test results, which is not currently widely available. Second, whether this approach leads to comparable efficacy with PI-based triple therapy in all patient subgroups with RVR, including those with advanced fibrosis, is unclear. Before recommending this strategy, appropriately designed randomized trials, including short duration triple therapy (eg, 12 weeks) and cost-effectiveness analyses (from a Canadian perspective) are necessary.

PATIENTS WITH HCV GENOTYPE 1 AND PREVIOUS TREATMENT FAILURE

HCV-infected individuals who have failed to obtain an SVR to IFN-based treatment can be categorized into three groups based on viral kinetics during their previous course of therapy: relapsers, partial responders and null responders (Table 4). Because most treatment-experienced patients in Canada have failed dual therapy with PEG-

IFN and RBV, the remainder of this discussion refers to this subgroup. Retreatment of treatment-experienced patients infected with HCV genotype 1 using either boceprevir or telaprevir, along with PEG-IFN and RBV, has been studied in two phase 3 trials (8,9).

Boceprevir

In the Retreatment with HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol 2 (RESPOND-2) trial (9), relapsers and partial responders were randomly assigned to one of three treatment groups; null responders were not included in this study. All patients were initially treated with a four-week lead-in period of PEG-IFN-alpha-2b and RBV. Patients in the control arm received an additional 44 weeks of PEG-IFN and RBV. In the RGT arm, individuals who achieved undetectable HCV RNA levels by week 8 and remained undetectable through week 12 (compared with week 24 in the treatment-naive study) were assigned triple therapy until week 36. Those with persistently detectable HCV RNA at week 8 received triple therapy to week 36 followed by an additional 12 weeks of PEG-IFN and RBV dual therapy. Finally, patients in the FIXED group received 44 weeks of triple therapy after the four-week lead-in period. All patients with detectable HCV RNA at treatment week 12 were discontinued from treatment due to futility. Of note, the Canadian product monograph for boceprevir recommends a different stopping rule to avoid missing individuals who may achieve an SVR (78,83). Specifically, all treatment should be discontinued in patients with HCV RNA ≥100 IU/mL at week 12 or detectable HCV RNA at week 24 (78).

In terms of efficacy, the overall SVR in the control group was 21% compared with 59% in the RGT arm and 66% in the FIXED arm (9). Boceprevir-treated patients were more likely to achieve SVR than those who received dual therapy; however, the difference between the RGT and FIXED arms was not statistically significant. SVR rates among previous relapsers were 29% in the control arm versus 69% and 75% in the RGT and FIXED boceprevir arms, respectively. Corresponding SVR rates among partial responders were 7%, 40% and 52%, respectively. Because null responders were not included in RESPOND-2, a subsequent study (PROVIDE) evaluated the success of triple therapy including boceprevir among 48 patients who failed to achieve at least a 2 $\log_{10}$ reduction in HCV RNA after 12 weeks of dual therapy from the control arms of SPRINT-2 and RESPOND-2 (84). In a preliminary report, an SVR was reported in 38% of patients; additional data are forthcoming. Based on these data, Health Canada and the United States Food and Drug Administration have approved boceprevir for the treatment of previous null responders.

Telaprevir

Telaprevir therapy for the retreatment of patients with HCV genotype 1 who failed to respond to dual therapy was evaluated in the Re-treatment of Patients with Telaprevir-based Regimen to Optimize Outcomes (REALIZE) phase 3 study (8). As in the RESPOND-2 trial, there were three treatment groups. The first group received a four-week lead-in period of PEG-IFN-alpha-2a and RBV, followed by 12 weeks of triple therapy including telaprevir and an additional 32 weeks of dual therapy. The second group received 12 weeks of triple therapy followed by 36 weeks of dual therapy (ie, no lead-in), and the control arm received 48 weeks of dual therapy. RGT was not assessed in this study. Telaprevir was discontinued in patients with HCV RNA >100 IU/mL at weeks 4, 6 or 8; PEG-IFN and RBV were continued in this situation. All treatment was discontinued in individuals with <2 $\log_{10}$ decrease in HCV RNA level at week 12 in the telaprevir group with no lead-in (arm 2) and in the control group (arm 3); at week 16 in the telaprevir group that received a lead-in (group 1); and in all patients with detectable HCV RNA at weeks 24 or 36. Of note, the stopping rules in this study differ from those listed in the Canadian product monograph for telaprevir, which recommends discontinuation of all therapy if HCV RNA exceeds 1000 IU/mL at week 4 or 12, or is detectable at week 24 (the same criteria recommended for treatment-naïve individuals) (80).

Overall, the SVR rate in the control group was 17% compared with 66% in telaprevir-treated patients who received a lead-in (group 1) and 64% in those who started telaprevir immediately (group 2). The response rates did not differ between the two telaprevir-containing regimens (8). In subgroup analyses according to previous treatment response, relapsers demonstrated excellent responses with an SVR observed in 86% of telaprevir-treated patients compared with 24% among controls. In partial responders, SVR rates were 57% with telaprevir and 15% among controls. Among previous null-responders, SVR rates were 31% with telaprevir compared with only 5% among controls.

Although RGT was not assessed in the REALIZE trial, data from phase 2 studies support this approach in previous relapsers treated with telaprevir (85,86). Specifically, 78% (52 of 67) of relapsers in these trials achieved eRVR with 12 weeks of telaprevir-based triple therapy, which was followed by PEG-IFN and RBV for 12 weeks. An SVR was observed in 94% (49 of 52) of these patients (87). For comparison, among relapsers with an eRVR in the REALIZE trial, an SVR rate of 96% (91 of 95) was observed with a regimen including 36 weeks of dual therapy after an initial 12 weeks of triple therapy (8).

Patients with cirrhosis

In the RESPOND-2 trial, 12% (n=39) of individuals treated with boceprevir had compensated cirrhosis (F4) (88). The rates of SVR among these individuals categorized according to previous treatment response are not available. However, cirrhotic patients treated with triple therapy for 48 weeks were more likely to experience an SVR (77%) than those treated with RGT (35%) (78). In patients with advanced fibrosis (F3 or F4), corresponding SVR rates were 68% and 44%, respectively. In the REALIZE study, 23% (n=137) of telaprevir-treated individuals had compensated cirrhosis at baseline (8). Compared with the control group, SVR rates among cirrhotic subjects who received telaprevir were 87% (48 of 55) versus 13% (two of 15) for relapsers, 34% (11 of 32) versus 20% (one of five) for partial responders, and 14% (seven of 50) versus 10% (one of 10) for null responders (80). In light of limitations in the available data, including the absence of an RGT arm in the REALIZE trial, retreatment of cirrhotic individuals with either boceprevir or telaprevir should include 48 weeks of total therapy. Although data are limited, patients with bridging fibrosis (F3) may also benefit from prolonged therapy, particularly because many of these patients may actually have cirrhosis (due to the error of fibrosis assessment using biopsy and other tools).

Recommendations:

26. Noncirrhotic patients with HCV genotype 1 who have demonstrated relapse to previous PEG-IFN and RBV therapy should be offered retreatment with RGT including PEG-IFN, RBV, and boceprevir or telaprevir. Previous partial responders can be offered RGT with triple therapy including boceprevir or 48 weeks of total therapy (ie, non-RGT) including telaprevir (Class 1, Level A). Recommended management algorithms are as follows:
    a. Boceprevir in relapsers and partial responders (Figures 4A and 4B): Use four weeks of lead-in therapy with PEG-IFN and RBV followed by the addition of boceprevir. If HCV RNA is undetectable at weeks 8 through 24, discontinue triple therapy at 36 weeks. If HCV RNA is detectable at week 8 and undetectable at week 24, discontinue triple therapy at 36 weeks and continue PEG-IFN and RBV dual therapy to week 48.
    b. Telaprevir in relapsers (Figure 5A and 5B): Use telaprevir, PEG-IFN and RBV triple therapy. If HCV RNA is undetectable at weeks 4 and 12 (ie, eRVR), use triple therapy for a total of 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 12 weeks (24 weeks total treatment). If HCV RNA is detectable at week 4 and/or 12, use triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).

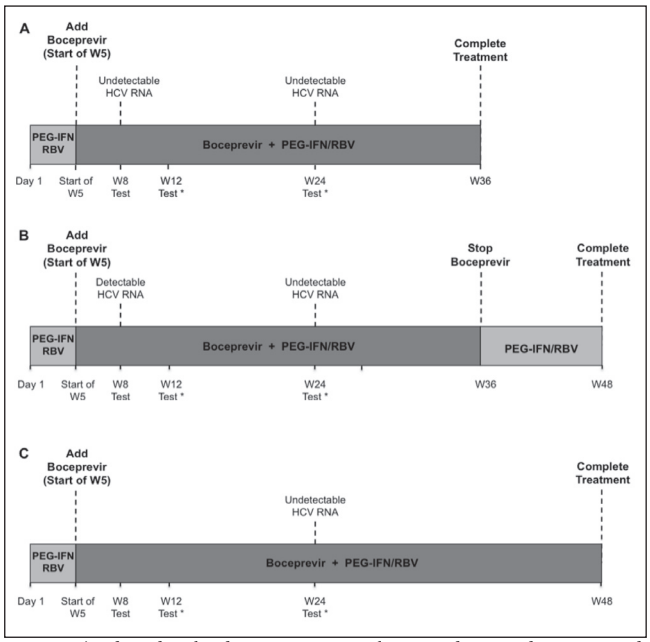


Figure 4) *Algorithm for the management of previously treated patients with hepatitis C virus (HCV) genotype 1 treated with pegylated interferon (PEG-IFN), ribavirin (RBV) and boceprevir.* **A** *Previous partial responders and relapsers who have an early response (defined as HCV RNA-negative at weeks 8 through 24) are eligible for response-guided treatment (RGT) (36 weeks total treatment).* **B** *Previous partial responders and relapsers who have a late response (defined as HCV RNA-positive at week 8) should not receive RGT (ie, treat for 48 weeks total).* **C** *Patients with a previous null response and those with cirrhosis (F4) regardless of previous response should receive 48 weeks of treatment (ie, not RGT).* *Indicates discontinuation of all treatment due to futility in patients with HCV RNA ≥100 IU/mL at treatment week 12 or detectable HCV RNA at week 24*

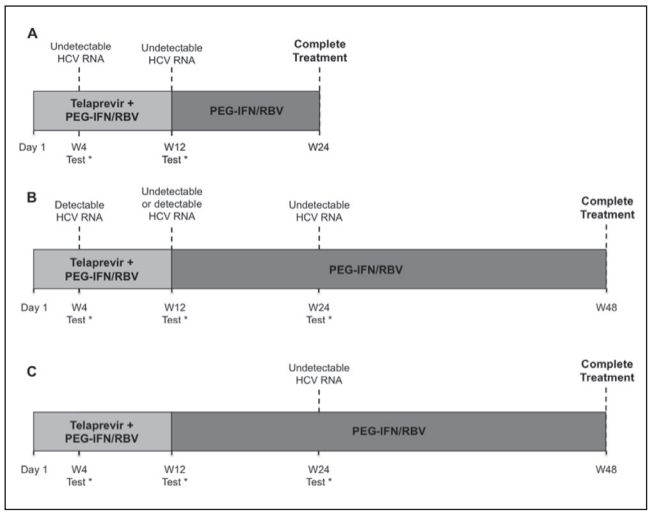


Figure 5) *Algorithm for the management of previously treated patients with hepatitis C virus (HCV) genotype 1 treated with pegimterferon (PEG-IFN), ribavirin (RBV) and telaprevir.* **A** *Patients with a previous relapse who achieve an extended rapid virological response (HCV RNA negative at weeks 4 and 12) are eligible for response-guided therapy (RGT) (24 weeks total treatment).* **B** *Patients with a previous relapse who do not achieve an extended rapid virological response should not receive RGT (ie, treat for 48 weeks total).* **C** *Patients with a previous partial response or null response, and those with cirrhosis (F4) regardless of previous response should receive 48 weeks of treatment (ie, not RGT).* *Indicates discontinuation of all treatment due to futility in patients with HCV RNA >1000 IU/mL at treatment weeks 4 or 12 or detectable HCV RNA at week 24*

c. Telaprevir in partial responders (Figure 5C): Use telaprevir, PEG-IFN and RBV triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).

27. Noncirrhotic patients with HCV genotype 1 who have demonstrated a null response to previous PEG-IFN and RBV therapy should be considered for triple therapy including PEG-IFN, RBV, and boceprevir or telaprevir (Class 1, Level B).
    a. Boceprevir in null responders (Figure 4C): Use 4 weeks of lead-in therapy with PEG-IFN and RBV followed by an additional 44 weeks of triple therapy including boceprevir (48 weeks total treatment).
    b. Telaprevir in null responders (Figure 5C): Use triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).
28. Treatment-experienced patients with HCV genotype 1 and cirrhosis should not be retreated with RGT (Class 3, Level B). Recommended management algorithms are as follows:
    a. Boceprevir (Figure 4C): Use four weeks of lead-in therapy with PEG-IFN and RBV followed by an additional 44 weeks of triple therapy including boceprevir (48 weeks total treatment).
    b. Telaprevir (Figure 5C): Use triple therapy for 12 weeks followed by PEG-IFN and RBV dual therapy for an additional 36 weeks (48 weeks total treatment).
29. In patients with HCV genotype 1 in whom the previous treatment response cannot be determined, the optimal management approach is unclear. In noncirrhotic patients, RGT as described for relapsers (see Recommendation 26) can be considered, although the risk of relapse may be increased compared with 48 weeks of treatment. Patients with cirrhosis should be treated for 48 weeks (Class 2b, Level C).
30. Futility rules (Table 7): Futility rules in patients with previous treatment failure are identical to those described for treatment-naïve patients (see Recommendations 19 and 25 above).

ADVERSE EVENTS OF TELAPREVIR AND BOCEPREVIR

Patients treated with PI-based combination therapy experience more adverse effects than those treated with PEG-IFN and RBV alone. There are no data to support switching from one PI to another as a strategy to manage toxicity.

The addition of boceprevir to PEG-IFN and RBV leads to an increased incidence of anemia. In the phase 3 trials, hemoglobin levels fell below 100 g/L in 49% of patients receiving boceprevir compared with 29% of those on dual therapy. Severe anemia (hemoglobin <85 g/L) was reported in 9% of boceprevir-treated patients and 3% required transfusions (5,88). Hemoglobin level typically reaches a nadir on average 10 g/L to 15 g/L lower than with dual therapy at four to eight weeks after starting boceprevir (and telaprevir) and resolves on discontinuation of therapy (78,89). In the phase 3 trials of boceprevir, anemia was managed with RBV dosage reduction (by 200 mg decrements) and/or erythropoietin supplementation. Erythropoietin (provided by the study sponsor) was used in 44% of boceprevir-treated patients compared with 24% of control subjects (5,88). SVR rates were higher among patients with a significant decline in hemoglobin

concentration, likely due to increased RBV exposure. Moreover, similar SVR rates were observed between anemic patients managed with RBV dose reduction and those who received erythropoietin (or both) (90). While anemia is reversible with discontinuation of boceprevir, the dosage of boceprevir should not be reduced for anemia because of the increased risk of antiviral drug resistance in the setting of subtherapeutic drug exposure. Patients treated with boceprevir also reported a higher rate of dysgeusia compared with controls (approximately 40% versus approximately 20%) (5,88).

The addition of telaprevir to PEG-IFN and RBV led to an increased incidence of anemia, dermatological side effects and gastrointestinal symptoms (eg, nausea and diarrhea). In the phase 3 trials, hemoglobin levels <100 g/L were reported in 41% of telaprevir-treated patients compared with 22% of controls (6-8). Severe anemia (<85 g/L) was reported in 9% of telaprevir-treated patients. Risk factors for anemia include older age, lower baseline hemoglobin and BMI, more advanced fibrosis and genotype 1b infection (91). Because erythropoietin use was not permitted in these trials, anemia was managed mainly with RBV dose reductions. Neither anemia nor RBV dose reduction had a detrimental impact on treatment response to telaprevir-based therapy (92). Because RBV dose modifications followed the product monograph (ie, first decrease to 600 mg/day), this degree of RBV dose modification (versus the typical standard of 200 mg decrements) is the preferred approach to anemia management in patients treated with telaprevir. Clinical trial and postmarketing experience suggest that the transfusion of packed red blood cells is more frequently required to manage severe symptomatic anemia in patients undergoing PI-based therapy (both boceprevir and telaprevir), particularly those with cirrhosis (93). In the REALIZE trial, 7% of patients treated with telaprevir required blood transfusions compared with <1% in the control arm (8).

Rash was reported in 56% of telaprevir-treated patients compared with 32% of controls (6,8). The rash associated with telaprevir was typically eczematous and maculopapular in nature, usually occurred within the first four weeks of therapy, and resolved with drug discontinuation. Although most rashes were mild to moderate, severe rashes (affecting >50% of the body surface area) occurred in 6% of patients. Stevens-Johnson syndrome and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome – both potentially lethal complications – occurred in fewer than 1% of telaprevir-treated patients, but no deaths were reported in the trials. Severe rash necessitates prompt drug discontinuation and dermatology consultation. If telaprevir is discontinued early due to rash, PEG-IFN and RBV treatment can continue. Patients treated with telaprevir also reported a higher incidence (29%) of anorectal symptoms including pain, burning and pruritus. These symptoms did not lead to drug discontinuation and generally responded to topical therapies (6,8).

Recommendations:

31. Close monitoring of hemoglobin levels is essential during antiviral treatment for HCV, particularly during the administration of PIs (Class 1, Level C).
32. Management of anemia may include any of the following strategies: RBV dose reduction (Class 1, Level A), transfusion of packed red blood cells (Class 1, Level C), and/or erythropoietin administration (Class 2a, Level C).

ANTIVIRAL RESISTANCE

Emergence of antiviral-resistant variants during PI-based treatment has been reported in all trials and is associated with incomplete virological response, virological breakthrough and relapse. Due to the high replication rate of HCV and the low fidelity of its RNA-dependent RNA polymerase, these variants are present at low frequencies before DAA exposure. Indeed, pretreatment testing in phase 3 trials of boceprevir and telaprevir has confirmed the presence of these variants in 5% to 7% of patients using poorly sensitive methods (ie, population sequencing) (5,6). Because pre-existing variants do not appear to impact the probability of SVR or treatment decisions with the first-generation PIs, routine pretreatment resistance testing is not recommended.

In the SPRINT-2 and ADVANCE trials of treatment-naive patients, antiviral-resistant variants emerged in 16% and 12% of patients treated with boceprevir and telaprevir, respectively (5,6). Similar viral variants, which are clustered around the catalytic site of the NS3/4A serine protease, are selected during treatment with both agents suggesting cross-resistance between PIs. In these studies, the majority of patients (80% to 90%) who experienced incomplete viral suppression, breakthrough or relapse on treatment cessation harboured resistant variants. However, resistance testing is not needed in cases of treatment failure because the results will not influence subsequent patient management. HCV genotype 1a has a higher risk of resistance than genotype 1b due to the higher genetic barrier of the latter subtype (39,40). Moreover, the emergence of antiviral resistance is inversely related to IFN responsiveness. For example, in the SPRINT-2 trial of boceprevir, resistance-associated variants were identified in 46% of patients with <1 $\log_{10}$ decrease in HCV RNA during the lead-in phase versus only 5% of patients with greater virological suppression (5).

The clinical implications of emergent antiviral resistance, including implications for the future selection of DAAs and the success of retreatment, are unclear. During longitudinal follow-up of patients who developed antiviral resistance in the telaprevir phase 2/3 trials, 17% had persistent resistant variants documented by population sequencing after a median follow-up period of 29 months (40). Among patients treated with boceprevir, 25% of such subjects still had at least one substitution detected by population sequencing after 2.5 years of follow-up (89). Because population sequencing can only detect variants that represent at least 20% of the population of circulating virus, it is possible that patients who test negative by this technique still harbour a significant quantity of resistant variants. The clinical significance of 'disappearance' of resistance by population sequencing after stopping therapy remains unclear because data on retreatment of such patients are not available. Despite these uncertainties, every effort should be made to minimize the development of antiviral resistance. Patients who meet futility rules indicating a high likelihood of treatment failure (Table 7) should discontinue therapy immediately, and dosage reductions of boceprevir and telaprevir should not be utilized to manage treatment-related side effects. Finally, PIs cannot be used alone and, therefore, should be stopped if either PEG-IFN or RBV are discontinued.

Recommendations:

33. To reduce the development of antiviral resistance to the PIs, patients who meet futility rules indicating a high likelihood of treatment failure should discontinue therapy immediately (Class 1, Level A).
34. Dosage reductions of boceprevir and telaprevir should not be utilized to manage treatment-related side effects (Class 2a, Level C).
35. To prevent resistance, PIs must be stopped if either PEG-IFN or RBV are discontinued (Class 1, Level A).

DRUG-DRUG INTERACTIONS

Before the initiation of boceprevir or telaprevir, potential drug-drug interactions 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. Boceprevir is primarily metabolized by aldo-keto reductase, partially metabolized by cytochrome P450 (CYP3A4/5), and is a potent inhibitor of CYP3A4/5 activity. Therefore, boceprevir is contraindicated with medications that are potent inducers of CYP3A4/5 (that would reduce plasma concentrations and the therapeutic effect of boceprevir) and those that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated

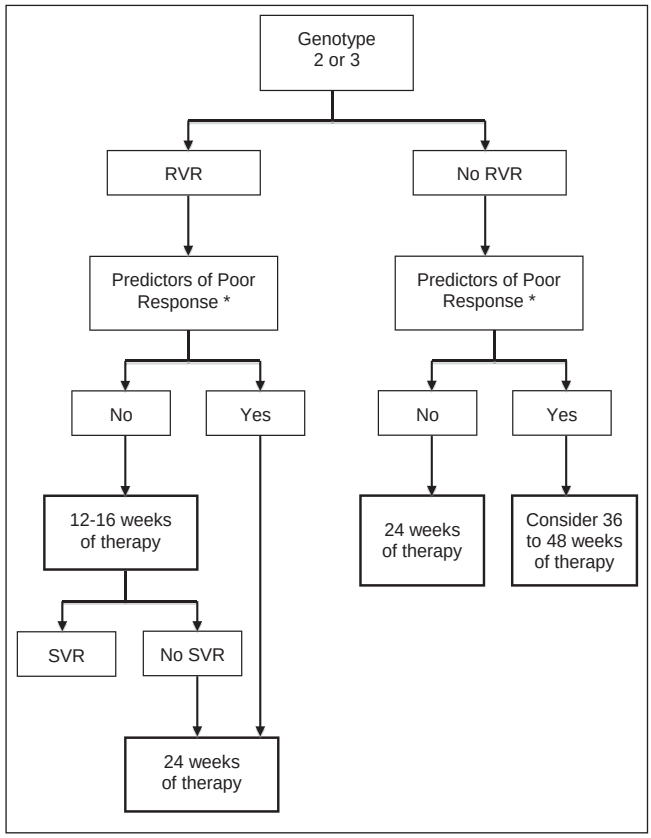


Figure 6) *Algorithm for the management of previously untreated patients with hepatitis C genotypes 2 or 3 treated with peginterferon and ribavirin therapy. *Predictors of poor response to therapy include advanced fibrosis, black race, obesity and metabolic syndrome/insulin resistance. Shortened treatment (12 to 16 weeks) in patients with rapid virological response (RVR) should be restricted to those treated with weight-based ribavirin dosing. SVR Sustained virological response*

with serious and/or life-threatening events (narrow therapeutic index) (78). Telaprevir is primarily metabolized by CYP3A4 and is an inhibitor of CYP3A and P-glycoprotein. Therefore, telaprevir is contraindicated when combined with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Telaprevir should not be administered with drugs that strongly induce CYP3A and, thus, may lead to lower exposure and loss of efficacy.

Medications with potential drug-drug interactions with boceprevir or telaprevir are numerous and include the following classes: antiarrhythmics, anticoagulants, anticonvulsants, antihistamines, antibacterials, antiretrovirals, statins, herbal products (eg, St John's Wort), immunosuppressants, phosphodiesterase inhibitors and some sedatives/hypnotics. Due to an interaction between the PIs and oral contraceptives that can reduce the efficacy of the latter, a second method of contraception should be used during treatment with these agents. Because a complete listing of these agents is beyond the scope of these guidelines, and because knowledge regarding possible drug-drug interactions is constantly evolving, the reader is referred to the appropriate product monographs (78,80) and updated online databases (eg, www.hep-druginteractions.org).

TREATMENT-NAIVE PATIENTS WITH HCV GENOTYPES OTHER THAN 1

Since the last Canadian guidelines on the management of hepatitis C were published in 2007 (4), the treatment of patients with genotypes other than 1 has not changed substantially. In these patients, the combination of PEG-IFN and RBV remains the standard therapy because data documenting a beneficial effect of the PIs on non-1 genotypes are limited. The treatment of these patients should consider on-treatment viral kinetics and patient-related factors that influence treatment response including the severity of fibrosis, race, obesity, metabolic syndrome/insulin resistance and viral load. The utility of IL28B genotyping in patients with non-1 genotypes (except genotype 4) is limited (73-76). The following are general recommendations for the treatment of previously untreated patients with HCV genotypes other than 1.

Recommendations for patients with genotypes 2 or 3 (Figure 6):

36. Patients with genotypes 2 or 3 should be treated with either of the following: PEG-IFN-alpha-2a (Pegasys RBV, Hoffmann-La Roche Ltd, Canada) 180 µg subcutaneously once weekly and RBV 800 mg per day given orally in two divided doses; or PEG-IFN-alpha-2b (Pegetron, Merck & Co, Inc, Canada) 1.5 µg/kg subcutaneously once weekly and weight-based RBV (600 mg to 1400 mg per day given orally in two divided doses) (Class 1, Level A).
37. The standard duration of therapy in patients with genotypes 2 or 3 is 24 weeks. Patients who do not achieve EVR should discontinue therapy at week 12 (Class 1, Level A).
38. In patients with genotypes 2 or 3 who achieve an RVR with PEG-IFN and weight-based RBV therapy, shortening of treatment to 12 to 16 weeks can be considered. Abbreviated treatment should not be considered in patients with cofactors that reduce the likelihood of treatment success (eg, advanced fibrosis, black race, obesity, metabolic syndrome/insulin resistance) even if an RVR is achieved. If a patient relapses following a shortened course of treatment, retreatment for 24 weeks should be considered (Class 1, Level A).
39. In patients with genotype 3 who do not achieve an RVR but have an EVR, extending treatment to 36 to 48 weeks may be considered, particularly in the setting of cofactors that reduce the likelihood of treatment success (Class 2a, Level C).

Recommendations for patients with genotypes 4 to 6:

40. Patients with genotypes 4 to 6 should be treated with either of the following: PEG-IFN-alpha-2a (Pegasys RBV, Hoffmann-La Roche Ltd, Canada) 180 µg subcutaneously once weekly and RBV 1000 mg (if weight <75 kg) to 1200 mg (if weight ≥75 kg) per day given orally in two divided doses; or PEG-IFN-alpha-2b (Pegetron, Merck & Co, Inc, Canada) 1.5 µg/kg subcutaneously once weekly and RBV 600 mg/day to 1400 mg/day given orally in two divided doses (Class 1, Level A).
41. The standard duration of therapy in patients with genotypes 4 to 6 is 48 weeks. Treatment should be discontinued in patients who do not achieve an EVR at week 12 or if HCV RNA remains detectable at week 24 (Class 1, Level A).
42. Patients with genotype 4 who have mild fibrosis (METAVIR F0 to F2) and low baseline viral load (<800,000 IU/mL) can be treated for 36 weeks (Class 1, Level B).

PATIENTS WITH GENOTYPES OTHER THAN 1 AND PREVIOUS TREATMENT FAILURE

Data describing the retreatment of patients with non-1 genotypes who have failed a previous course of PEG-IFN and RBV are limited. However, data from the EPIC study provide evidence to consider retreatment of patients with HCV genotypes 2 or 3 and at least moderate fibrosis (METAVIR F2 to F4) (94). In this study, retreatment with PEG-IFN-alpha-2b and weight-based RBV for 48 weeks led to an SVR in 57% of relapsers and 36% of nonresponders (detectable HCV RNA at the end their previous therapy). Overall SVR rates in genotype 2/3-infected patients with F2, F3 and F4 fibrosis (irrespective of previous treatment response) were 55%, 55% and 45%, respectively (94). There are currently

no data to support retreatment of these patients with triple therapy including a DAA.

Recommendations:

43. In patients with genotypes 2 or 3 who have failed a previous 24-week course of PEG-IFN and RBV and have at least stage 2 fibrosis, retreatment with a 48-week course of PEG-IFN and RBV may be considered (Class 1, Level B).

OPTIMIZING TREATMENT SUCCESS

Adherence

Adherence to PEG-IFN and RBV dual therapy and triple therapy including PIs is associated with improved rates of SVR (95,96). Failure to adhere to the recommended treatment schedules and stopping rules when using the PIs may also increase the risk of resistance. Numerous characteristics of these regimens have a negative impact on adherence including the necessity to take multiple medications for prolonged periods, by different routes of administration and with numerous adverse effects. Several features of the first-generation PIs will add further treatment complexity including the increased pill burden (up to 12 extra pills per day), different dosing schedules (three times daily versus twice daily dosing), additional adverse effects, specific dietary constraints and potentially dangerous drug-drug interactions. Importantly, experts in multidisciplinary settings have treated the vast majority of individuals that have received these medications to date.

Recommendations:

44. Adherence to treatment and to futility rules, and close monitoring of concomitant drugs and side effects are particularly important with PI-based therapy. Optimal management of this population should be conducted by well-trained, experienced personnel.

Body weight

Numerous studies have suggested that increased body weight, and particularly, high BMI, is associated with accelerated fibrosis progression in the setting of chronic hepatitis C (97). Some (98,99), but not all (33), studies also suggest that increased body weight has a negative impact on the probability of SVR to dual therapy with PEG-IFN and RBV. With combination therapy including telaprevir or boceprevir, obesity does not appear to significantly influence treatment responses (5,6). In light of these findings, specific recommendations for weight loss before PI-based therapy in an attempt to improve rates of SVR (as has been advocated by some for dual therapy [100]) cannot be made.

Erythropoietin for treatment-induced anemia

Anemia remains a common adverse effect of all currently available anti-HCV therapies. A significant proportion of the decrease in hemoglobin levels is due to RBV, which is likely to remain one of the cornerstones of HCV therapy even with the development of IFN-free regimens. As previously described, the addition of boceprevir or telaprevir to PEG-IFN and RBV is associated with an increased incidence and severity of anemia. In the phase 3 trials evaluating boceprevir, erythropoietin was administered to approximately 40% of patients (5,88). Erythropoietin administration has been shown to improve hemoglobin levels during therapy, reduce requirements for RBV dose reduction, and improve the quality of life of patients undergoing PEG-IFN and RBV treatment (101,102), but there is no definitive evidence that its use increases the likelihood of SVR (90). Nevertheless, erythropoietin may be considered in anemic patients who have not responded adequately to RBV dose reduction.

Neutropenia

Neutropenia is a common complication of IFN-based therapy, particularly among African-Americans and patients with cirrhosis, and is the leading indication for PEG-IFN dose reduction (98,99). Triple therapy including boceprevir (not telaprevir) further increases the risk of neutropenia (79,89). However, there is no evidence that treatment-induced neutropenia is associated with an increased risk of infection in individuals receiving anti-HCV therapy (103,104). Similarly, the use of granulocyte-colony stimulating factor has not been shown to reduce the incidence of on-treatment infections or improve rates of SVR (105). Therefore, there is insufficient evidence to recommend the use of granulocyte-colony stimulating factor to manage neutropenia during HCV therapy.

Thrombocytopenia

Thrombocytopenia is observed in up to 25% of individuals with HCV; most cases are mild to moderate in severity (106,107). Severe thrombocytopenia (platelets $<40\times10^9$/L) is most often observed in patients with cirrhosis and portal hypertension. While treatment with PEG-IFN and RBV often causes or exacerbates pre-existing thrombocytopenia, bleeding complications are rare and platelet counts often improve following successful antiviral treatment (108,109). Triple therapy including boceprevir or telaprevir is associated with an increased incidence of thrombocytopenia (78,80). The Canadian product monographs for PEG-IFN-alpha-2a and -2b advise caution when starting antiviral therapy in patients with platelet counts less than 90×10^9/L to 100×10^9/L, and recommend PEG-IFN dosage reduction and discontinuation if platelets fall below 50×10^9/L and 25×10^9/L, respectively. These limits have been challenged by experts who suggest that PEG-IFN dose reductions are not necessary until the platelet count falls below 30×10^9/L, with discontinuation if the platelets fall below 20×10^9/L (4).

Eltrombopag, a thrombopoietin receptor agonist, is licensed in Canada for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. It has also been studied in HCV-infected patients with thrombocytopenia. When administered before PEG-IFN and RBV therapy, eltrombopag can increase platelet counts and, thus, increase patient eligibility for treatment (110). A recent phase 3, randomized controlled trial (Eltrombopag to iNitiate and maintain interferon Antiviral treatment to Benefit subjects with hepatitis C related Liver diseasE [ENABLE 1]) reported that the use of eltrombopag led to improved SVR to PEG-IFN and RBV therapy in patients with pretreatment platelet counts $<75\times10^9$/L (111). SVR rates in the eltrombopag and control arms were 23% and 14%, respectively. The utility of eltrombopag in patients receiving PI-based triple therapy is unknown. Importantly, eltrombopag has been associated with an increased risk of liver dysfunction and thrombotic complications, including portal venous thrombosis. In light of the absence of data with DAAs, potential complications and lack of regulatory approval for this indication, there are insufficient data to recommend use of this treatment.

Vitamin D deficiency

Several small studies have described an increased prevalence of vitamin D deficiency among patients with HCV infection, particularly those with advanced liver disease (112-114). There are some data suggesting that vitamin D deficiency impairs the response to anti-HCV therapy (114,115) and unconvincing evidence that vitamin D supplementation improves SVR rates to PEG-IFN and RBV therapy (114,116). Based on these limited data, additional studies are necessary regarding the role of vitamin D deficiency, testing and supplementation in HCV patients before any definitive recommendations can be made.

TREATMENT OF HCV IN ACTIVE ILLICIT DRUG USERS

In Canada, the majority of new cases of HCV infection occur among users of illicit drugs (except cannabis). The relative importance of this population – which is estimated to represent more than 60% of prevalent cases and 75% of incident cases in Canada – is expected to grow in the future (15). These patients have a high prevalence of psychiatric disease, medical comorbidities (including HIV and hepatitis B virus coinfections), and face significant social challenges such as

homelessness and lack of supports (117,118). As a result, most individuals with HCV in this population remain untreated (119,120). The last 2007 Canadian consensus guidelines recommended that research funds be allocated to improve care strategies for HCV-infected illicit drug users (4). Since then, reports have shown that it is feasible to offer PEG-IFN and RBV therapy to these patients under the supervision of experienced physicians (121-123). Evidence obtained from these trials has demonstrated that properly selected HCV-infected IDUs can achieve SVR rates comparable to those of non-IDU populations (124). This strategy has also shown lower than expected risk of HCV reinfection, possibly due to a combination of a change in risk-taking behaviours (possibly related to successful engagement in care) and acquired immunological protection (125-127).

Recommendations:

45. All patients with a past or present history of illicit drug use should be screened for hepatitis B, hepatitis C and HIV (Class 1, Level C).
46. Any HCV-infected individual with a past history of illicit drug use should be considered for treatment as per any other individual according to the current guidelines (Class 1, Level B).
47. The decision to treat HCV-infected IDUs with recent or ongoing illicit drug use should be made on an individualized basis by experienced physicians, ideally in a multidisciplinary setting. Treatment of substance abuse and mental health comorbidities and optimization of social conditions should be implemented to enhance the outcomes of anti-HCV therapy. Teaching and implementation of harm-reduction strategies is an integral component of the global care of these patients (Class 1, Level C).

TREATMENT OF HCV IN OTHER SPECIAL POPULATIONS

There are limited data describing the utility of first-generation PIs in many 'special' populations that have the greatest need for treatment (eg, patients with decompensated cirrhosis, post-liver transplantation, and HIV/HCV coinfection). These patients have the most aggressive disease, yet the lowest probability of success with PEG-IFN and RBV therapy. Studies are ongoing to evaluate the safety and efficacy of boceprevir and telaprevir in these patient populations. Particular attention will be necessary to avoid drug-drug interactions, especially between the PIs and immunosuppressants in post-transplant patients and antiretrovirals in those with HIV/HCV coinfection. It is also expected that adverse events, particularly anemia, will be more prevalent among these high-risk subgroups. Preliminary data suggest that SVR rates among HIV/HCV coinfected patients treated with triple therapy including boceprevir or telaprevir are comparable with those observed in HCV monoinfected patients (128,129). However, until further data are available, treatment of these special populations should be restricted to experienced centres. Highly selected patients with decompensated cirrhosis should only be treated in centres with access to liver transplantation. The efficacy and safety of these agents in pediatric patients and those with acute HCV infection is unknown.

ACKNOWLEDGEMENTS: This consensus guideline was produced in collaboration with the Organizing Committee (Drs Robert Bailey, Robert Myers, Kevork Peltekian and Winnie Wong) and the general membership of CASL, who provided extensive peer review of the manuscript. The authors acknowledge all participants at the consensus conference including invited speakers (Drs Brian Conway, Paul Marotta, Linda Scully, Morris Sherman, Philip Wong and Eric Yoshida), session chairs (Drs Mel Krajden and Lawrence Worobetz), and the discussion panel (Drs Curtis Cooper, Marc Deschenes, Mang Ma, Carla Osiowy, Bernard Willems and Helga Witt-Sullivan). Special thanks to the Canadian Liver Foundation for providing unrestricted funding for the conference and the conference secretariat, Buksa Associates Inc (Jacqueline Solc and Rebecca Swanson). Finally, the authors thank Dr Jean-Michel Pawlotsky for helpful comments regarding the manuscript.

DISCLOSURES: The authors report the following potential conflicts of interest. **Dr Marc Bilodeau:** Consulting fees from Merck Canada Inc, Vertex and GlaxoSmithKline. Speaking fees from Merck Canada Inc, Novartis and Astellas. Research support from the Canadian Liver Foundation, Merck Canada Inc and Novartis; **Dr Jordan Feld:** Consulting fees from Merck Canada Inc, Roche Canada, Johnson and Johnson, Vertex, Abbott Laboratories and Gilead Sciences. Speaking fees from Merck Canada Inc and Abbott Laboratories; **Dr Robert Myers:** Consulting fees from Merck Canada Inc, Roche Canada, Genentech Inc, Johnson and Johnson, Norgine Ltd, GE Healthcare and Vertex. Speaking fees from Merck Canada Inc, Roche Canada, Vertex and KNS Canada. Research support from the Canadian Institutes for Health Research, Alberta Heritage Foundation for Medical Research (now Alberta Innovates-Health Solutions) and Echosens; **Dr Alnoor Ramji:** Consulting fees from Merck Canada Inc, Roche Canada, Bristol-Myers Squibb, Gilead Sciences, AstraZeneca and Vertex. Speaking fees from Merck Canada Inc, Roche Canada, Bristol-Myers Squibb, Gilead Sciences, AstraZeneca, Amgen, Vertex and Abbott Laboratories; **Dr Stephen Wong:** Consulting fees from Merck Canada Inc, Roche Canada and Vertex. Speaking fees from Merck Canada Inc and Roche Canada.

REFERENCES

1. American Heart Association. <http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf> (Accessed February 1, 2012).
2. 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;139:493-8.
3. 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.
4. Sherman M, Shafran S, Burak K, et al. Management of chronic hepatitis C: Consensus guidelines. Can J Gastroenterol 2007;21(Suppl C):25C-34C.
5. 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.
6. 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.
7. 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.
8. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-28.
9. 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.
10. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:798-801.
11. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 2009;461:399-401.
12. 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;204:1391-4.
13. 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.
14. 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.

15. Remis RS. Modelling the incidence and prevalence of hepatitis C infection and its sequelae in Canada, 2007. Final Report. Public Health Agency of Canada. <www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf> (Accessed February 1, 2012).
16. 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.
17. Martinot-Peignoux M, Stern C, Maylin S, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology 2010;51:1122-6.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509-16.
27. 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.
28. Kronenberger B, Zeuzem S. New developments in HCV therapy. J Viral Hepat 2012;19(Suppl 1):48-51.
29. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med 2002;136:288-92.
30. Doucette KE, Robson V, Shafran S, Kunimoto D. Improving access to care by allowing self-referral to a hepatitis C clinic. Can J Gastroenterol 2009;23:421-4.
31. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513-21.
32. 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.
33. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-93.
34. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology 2004;127:1724-32.
35. Puoti C, Magrini A, Stati T, et al. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. Hepatology 1997;26:1393-8.
36. Allen SA, Spaulding AC, Osei AM, Taylor LE, Cabral AM, Rich JD. Treatment of chronic hepatitis C in a state correctional facility. Ann Intern Med 2003;138:187-90.
37. Martin CK, Hostetter JE, Hagan JJ. New opportunities for the management and therapy of hepatitis C in correctional settings. Am J Public Health 2010;100:13-7.
38. 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.
39. 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.
40. 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 (Abst).
41. Bedossa P. Liver biopsy. Gastroenterol Clin Biol 2008;32:4-7.
42. 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.
43. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49:1017-44.
44. 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. doi:10.1002/hep.24515.
45. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1998;93:44-8.
46. 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.
47. Forns X, Ampurdanes S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology 2002;36:986-92.
48. 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.
49. Adams LA, Bulsara M, Rossi E, et al. Hepascore: An accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem 2005;51:1867-73.
50. Boursier J, Bacq Y, Halfon P, et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol 2009;21:28-38.
51. Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinterferon alfa-2b combination therapy for chronic hepatitis C. J Viral Hepatol 2009;16:178-86.
52. Parkes J, Guha IN, Roderick P, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. J Viral Hepat 2010;18:23-31.
53. Friedrich-Rust M, Ong MF, Martens S, et al. Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. Gastroenterology 2008;134:960-74.
54. 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 2010;24:661-70.
55. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepatol 2009;16:300-14.
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. Lucidarme D, Foucher J, Le Bail B, et al. Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C. Hepatology 2009;49:1083-9.
58. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. J Hepatol 2012;56:564-70.
59. Talwalkar JA, Yin M, Fidler JL, Sanderson SO, Kamath PS, Ehman RL. Magnetic resonance imaging of hepatic fibrosis: Emerging clinical applications. Hepatology 2008;47:332-42.
60. Friedrich-Rust M, Nierhoff J, Lupsor M, et al. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: A pooled meta-analysis. J Viral Hepat 2012;19:e212-e219.

61. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: New algorithms are more precise and entirely noninvasive. Hepatology 2012;55:58-67.
62. Sebastiani G, Halfon P, Castera L, et al. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. Aliment Pharmacol Ther 2012;35:92-104.
63. 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;140:1970-9,1979 e1971-1973.
64. Ngo Y, Munteanu M, Messous D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem 2006;52:1887-96.
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. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology 2010;139:120-9, e118.
68. Poordad F, Bronowicki JP, Gordon SC, et al. IL28B polymorphism predicts virologic response in patients with hepatitis C genotype 1 treated with boceprevir combination therapy. J Hepatol 2011;54(Suppl 1):S6.
69. Jacobson IM, Catlett I, Marcellin P, et al. Telaprevir substantially improves SVR rates across all IL28B genotypes in the ADVANCE trial. J Hepatol 2011;54(Suppl 1):S1369.
70. Pol S, Aerssens J, Zeuzem S, et al. Similar SVR rates in IL28B CC, CT or TT prior relapser, partial- or null-responder patients treated with telaprevir/peginterferon/ribavirin: Retrospective analysis of the REALIZE study (Abstract 13). J Hepatol 2011;54(Suppl 1):S6.
71. Mangia A, Thompson AJ, Santoro R, et al. Limited use of interleukin 28B in the setting of response-guided treatment with detailed on-treatment virological monitoring. Hepatology 2011;54:772-80.
72. O'Brien TR. Interferon-alfa, interferon-lambda and hepatitis C. Nat Genet 2009;41:1048-50.
73. Asselah T, De Muynck S, Broet P, et al. IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. J Hepatol 2012;56:527-32.
74. De Nicola S, Aghemo A, Grazia Rumi M, et al. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. Hepatology 2012;55:336-42.
75. Mangia A, Thompson AJ, Santoro R, et al. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. Gastroenterology 2010;139:821-7, 827 e821.
76. Moghaddam A, Melum E, Reinton N, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. Hepatology 2011;53:746-54.
77. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med;364:1195-206.
78. Merck Canada Inc. Product monograph: Victrelis (boceprevir). <www.merckfrosst.ca/assets/en/pdf/products/VICTRELIS-PM_E.pdf> (Accessed February 1, 2012).
79. Department of Health and Human Services, Food and Drug Administration. Antiviral Products Advisory Committee: Telaprevir NDA briefing document. <www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/DrugsAntiviralDrugsAdvisoryCommittee/UCM252561.pdf> (Accessed February 1, 2012).
80. Vertex Pharmaceuticals (Canada) Incorporated. Product Monograph: Incivek (Telaprevir tablets). <http://pi.vrtx.com/files/canadapm_telaprevir_en.pdf> (Accessed February 1, 2012).
81. Sarrazin C, Zeuzem S. Resistance to direct antiviral agents in patients with hepatitis C virus infection. Gastroenterology 2010;138:447-62.
82. Moreno C, Deltenre P, Pawlotsky JM, Henrion J, Adler M, Mathurin P. Shortened treatment duration in treatment-naive genotype 1 HCV patients with rapid virological response: A meta-analysis. J Hepatol 2010;52:25-31.
83. Jacobson IM, Marcellin P, Zeuzem S, et al. Treatment week 12/24 stopping rules for boceprevir (BOC) combination therapy with peginterferon + ribavirin (PR): Exploratory analysis of SPRINT-2 and RESPOND-2 (Abstract 954). Hepatology 2011;54:808A.
84. Vierling JM, Flamm SL, Gordon SC, et al. Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: The PROVIDE study (Abstract 931). Hepatology 2011;54:796A (Abst).
85. McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med 2010;362:1292-303.
86. Berg T, McHutchison JG, Adda N, et al. SVR with telaprevir, peginterferon alfa-2a and ribavirin in HCV patietns with well-characterized prior null response, partial response, viral breakthrough or relapse after PR (Abstract 4). J Hepatol 2010;52(Suppl 1):S2.
87. Adda N, Muir A, Adiwijaya B, et al. Response-guided telaprevir combination treatment in genotype 1 chronic hepatitis C patients who had a prior relapse to peginterferon alfa-2a/ribavirin (Abstract 26). Can J Gastroenterol 2012;26 Suppl A:81A (Abst).
88. 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.
89. Food and Drug Administration Background Material for Boceprevir Advisory Committee Division of Antiviral Products (DAVP), April 27, 2011. <www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/AntiviralDrugsAdvisoryCommittee/ucm252341.pdf> (Accessed February 1, 2012).
90. Sulkowski MS, Poordad F, Manns MP, et al. Anemia during treatment with peginterferon alfa-2b/ribavirin with or without boceprevir is associated with higher SVR rates: Analysis of previously untreated and previous treatment-failure patients (Abstract 476). J Hepatol 2011;54(Suppl 1):S195-196.
91. Roberts S, Andreone P, Pol S, et al. Impact of anemia and ribavirin dose reduction on SVR to a telaprevir-based regimen in patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure in the phase III REALIZE study (Abstract 1368). Hepatology 2011;54:253A (Abst).
92. Sulkowski M, Reddy R, Afdhal NH, et al. Anemia had no effect on efficacy outcomes in treatment-naive patients who received telaprevir-based regimen in the ADVANCE and ILLUMINATE phase 3 studies (Abstract 477). J Hepatol 2011;54(Suppl 1).
93. Hezode C, Dorival C, Zoulim F, et al. Safety of telaprevir or boceprevir in combination with peginterferon alfa/ribavirin, in cirrhotic non responders. First results of the French Early Access Program (ANRS CO20-CUPIC) in real-life setting (HepDart 2011 Abstract 46). <www.informedhorizons.com/hepdart2011/pdf/FinalProgram&Abstract%20Book_HEPDART2011.pdf> (Accessed March 8, 2012).
94. Poynard T, Colombo M, Bruix J, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology 2009;136:1618-28.
95. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061-9.
96. Gordon SC, Lawitz EJ, Bacon BR, et al. Adherence to assigned dosing regimen and sustained virologic response among hepatitis C genotype 1 treatment-naive and PEG/ribavirin treatment-failures treated with boceprevir plus peginterferon alfa-2b/ribavirin (Abstract 428). J Hepatol 2011;54(Suppl 1):S173 (Abst).
97. Powell EE, Jonsson JR, Clouston AD. Steatosis: Co-factor in other liver diseases. Hepatology 2005;42:5-13.
98. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 2001;358:958-65.
99. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982.
100. Hickman IJ, Clouston AD, Macdonald GA, et al. Effect of weight reduction on liver histology and biochemistry in patients with chronic hepatitis C. Gut 2002;51:89-94.
101. Pockros PJ, Shiffman ML, Schiff ER, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. Hepatology 2004;40:1450-8.

102. Afdhal NH, Dieterich DT, Pockros PJ, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: A prospective, double-blind, randomized controlled study. Gastroenterology 2004;126:1302-11.
103. Cooper CL, Al-Bedwawi S, Lee C, Garber G. Rate of infectious complications during interferon-based therapy for hepatitis C is not related to neutropenia. Clin Infect Dis 2006;42:1674-8.
104. Soza A, Everhart JE, Ghany MG, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology 2002;36:1273-9.
105. Tandon P, Doucette K, Fassbender K, Vandermeer B, Durec T, Dryden DM. Granulocyte colony-stimulating factor for hepatitis C therapy-associated neutropenia: Systematic review and economic evaluation. J Viral Hepat;18:e381-93.
106. Louie KS, Micallef JM, Pimenta JM, Forssen UM. Prevalence of thrombocytopenia among patients with chronic hepatitis C: A systematic review. J Viral Hepat 2011;18:1-7.
107. Giannini EG, Savarino V. Epidemiology of thrombocytopenia in patients with chronic hepatitis C: More than meets the eye. J Viral Hepatol 2011;18:8-10.
108. Roomer R, Hansen BE, Janssen HL, de Knegt RJ. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. J Hepatol 2010;53:455-9.
109. Iga D, Tomimatsu M, Endo H, Ohkawa S, Yamada O. Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon-alpha therapy: Possible etiology of HCV-associated immune thrombocytopenia. Eur J Haematol 2005;75:417-23.
110. McHutchison JG, Dusheiko G, Shiffman ML, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 2007;357:2227-36.
111. Afdhal N, Dusheiko G, Giannini EG, et al. Final results of ENABLE 2, a phase 3, multicenter study of eltrombopag as an adjunct for antiviral treatment of hepatitis C virus-related chronic liver disease associated with thrombocytopenia (Abstract LB-3). Hepatology 2011;54(4 Suppl):1427A (Abst).
112. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci 2010;55:2624-2628.
113. Cacopardo B, Camma C, Petta S, et al. Diagnostic and therapeutical role of vitamin D in chronic hepatitis C virus infection. Front Biosci (Elite Ed) 2012;4:1276-86.
114. Petta S, Camma C, Scazzone C, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology 2010;51:1158-67.
115. Bitetto D, Fattovich G, Fabris C, et al. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. Hepatology 2011;53:1118-26.
116. Bitetto D, Fabris C, Fornasiere E, et al. Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. Transpl Int 2011;24:43-50.
117. Sylvestre DL, Litwin AH, Clements BJ, Gourevitch MN. The impact of barriers to hepatitis C virus treatment in recovering heroin users maintained on methadone. J Subst Abuse Treat 2005;29:159-65.
118. Strathdee SA, Latka M, Campbell J, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis 2005;40(Suppl 5):S304-12.
119. Mehta SH, Genberg BL, Astemborski J, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health 2008;33:126-33.
120. Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, Fischer B, Tyndall MW. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. J Viral Hepatol 2009;16:352-8.
121. Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. Hepatology 2004;40:120-4.
122. Grebely J, Raffa JD, Meagher C, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. J Gastroenterol Hepatol 2007;22:1519-25.
123. Jeffrey GP, MacQuillan G, Chua F, et al. Hepatitis C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. Hepatology 2007;45:111-7.
124. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: A review of the available evidence. Clin Infect Dis 2009;49:561-73.
125. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. Lancet 2002;359:1478-83.
126. Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. Clin Infect Dis 2004;39:1540-3.
127. Grebely J, Conway B, Raffa JD, Lai C, Krajden M, Tyndall MW. Hepatitis C virus reinfection in injection drug users. Hepatology 2006;44:1139-45.
128. Dieterich DT, Soriano V, Sherman KE, et al. Telaprevir in combination with pegylated interferon-a-2a+RBV in HCV/HIV-co-infected patients: A 24 week treatment interim analysis (19th Conference on Retroviruses and Opportunistic Infections 2012, Abstract 46). <www.retroconference.org/2012b/Abstracts/42969.htm> (Accessed March 8, 2012).
129. Sulkowski M, Pol S, Fainboim H, et al. Boceprevir + pegylated interferon + ribavirin for the treatment of HCV/HIV-co-infected patients: end of treatment (week-48) interim results (19th Conference on Retroviruses and Opportunistic Infections 2012, Abstract 47). <www.retroconference.org/2012b/Abstracts/44725.htm> (Accessed March 8, 2012).

THE ATTACHED IS EXHIBIT "I" TO THE

AFFIDAVIT OF HEATHER RUMBLE PETERSON

SWORN BEFORE ME THIS 1ST DAY OF APRIL,

2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

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).

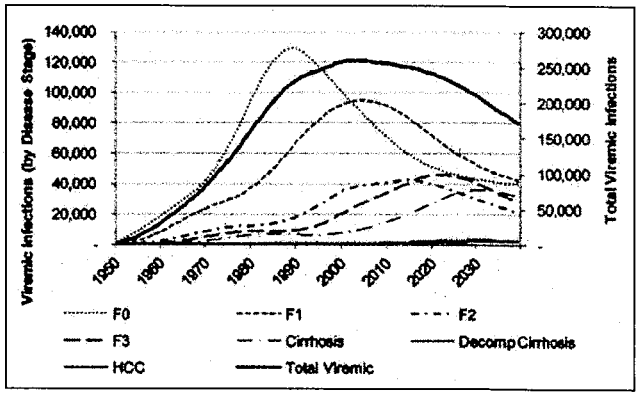


Figure 1) *Modelled incidence of hepatitis C-related sequelae in Canada, 1950 to 2035. Estimates are not mutually exclusive. Reproduced with permission from Myers et al (18). Decomp Decompensated; HCC Hepatocellular carcinoma*

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.

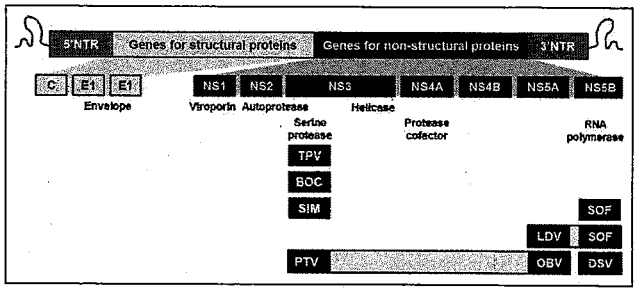


Figure 2) *Hepatitis C virus genome and the polyprotein targets of newly approved, direct-acting antiviral agents. Note: Sofosbuvir (SOF) is a nucleotide nonstructural protein (NS)5B polymerase inhibitor and dasabuvir (DSV) is a non-nucleoside polymerase inhibitor. BOC Boceprevir; LDV Ledipasvir; OBV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

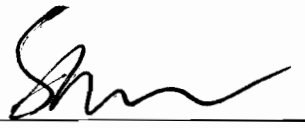
81. Bourliere M, Bronowicki JP, De Ledinghen V, et al. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy (Abstract LB-6). Hepatology 2014;60:13-4.
82. Bourliere M, Sulkowski M, Omata M, et al. 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.

THE ATTACHED IS EXHIBIT "J" TO THE

AFFIDAVIT OF HEATHER RUMBLE PETERSON

SWORN BEFORE ME THIS 1ST DAY OF APRIL,

2016



COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc.,
County of Essex, for Sutts, Strosberg LLP,
Barristers and Solicitors.
Expires February 18, 2019.

Claim ID	Approved at Level 3 meets the protocol with elevated ALT's	Was Interferon or Ribavirin taken?	Drug taken	Date Tran 2/ Hemo 2 Completed	Is there also a Fibroscan or Liver Biopsy result indicative of Non-Bridging Fibrosis	Date of HCV Treatment
21065	Y	N	N/A	Mar 20.14	N	N/A
1000325	Y	N	N/A	Jan 18.09	N	N/A
1401	Y	N	Simepevir/Sofosbuvir	May 30.13	N	May 15.14
20511	Y	N	N/A	Feb 5.13	N	N/A
21019	Y	N	N/A	May 7.14	N	N/A
1100268	Y	N	Harvoni	Dec 11.14	N	Feb 13.15
1401184	Y	Y	Boceprevir/Pegasys	Jun 8.12	N	Oct 19.12

THE ATTACHED IS EXHIBIT "K" TO THE AFFIDAVIT OF HEATHER RUMBLE PETERSON SWORN BEFORE ME THIS 1ST DAY OF APRIL, 2016

COMMISSIONER FOR TAKING AFFIDAVITS

Shelley Lynn Woodrich, a Commissioner, etc., County of Essex, for Sutts, Strosberg LLP, Barristers and Solicitors. Expires February 18, 2019.

Claim ID	Approved at Level 3 meets the protocol with CASL Guidelines	Was Interferon or Ribavirin taken?	Drug taken	Date Tran 2/ Hemo 2 Completed	Is there also a Fibroscan or Liver Biopsy result indicative of Non-Bridging Fibrosis?	Date of HCV Treatment
159	Y	N	Simiprevier & Sofosbuvir	Jul 29.14	N	Sep 24.14
242	Y	N	Unknown	Sep 10.13	N	Unknown
250	Y	N	Harvoni	Sep 9.15	N	Oct 14.15
482	Y	N	Harvoni	Oct 9.15	Y	Sep 3.15
581	Y	N	Harvoni	Sep 2.15	N	Nov 11.15
837	Y	N	Harvoni	Dec 11.14	N	Feb 6.15
1289	Y	N	Harvoni	Aug 28.15	N	Nov 24.15
1307	Y	N	Harvoni	Jan 20.15	Y	Feb 10.15
1543	Y	N	Harvoni	May 23.15	N	Aug 18.15
1578	Y	N	Harvoni	Oct 6.15	N	Nov 3.15
2219	Y	N	Harvoni	Sep 4.14	N	Unknown
2458	Y	N	Harvoni	Dec 9.14	N	Feb 6.15
2931	Y	N	Unknown	Mar 30.15	N	Unknown
3043	Y	N	Harvoni	Feb 12.15	N	July 18.15
3252	Y	N	Harvoni	Oct 2.14	N	Apr 2.15
3703	Y	N	Unknown	Aug 7.15	N	Unknown
3901	Y	N	Harvoni	Mar 3.15	N	Jun 11.15
4153	Y	N	Harvoni	May 5.15	N	Aug 27.15
4351	Y	N	Unknown	Jan 22.15	N	Unknown
4438	Y	N	Harvoni	Apr 7.15	Y	Dec 24.15
5021	Y	N	Unknown	Dec 17.15	Y	Unknown
5727	Y	Y	Pegasys	Jun 25.13	N	Sep 5.13
6113	Y	Y	Ribavirin	Mar 14.15	N	Jul 16.15
6823	Y	N	Harvoni	Sep 22.15	Y	Unknown
6833	Y	N	Harvoni	Dec 17.15	N	Unknown
6914	Y	N	Unknown	Jul 1.15	Y	Unknown
8046	Y	Y	Sovaldi/Pegasys	Nov 27.12	N	Apr 7.14
8114	Y	N	Simiprevier & Sofosbuvir	Apr 25.14	N	May 29.14
10926	Y	Y	Holkira Pak	Apr 6.15	Y	Jun 3.15
11072	Y	N	Harvoni	Feb 11.15	Y	Unknown
11347	Y	N	Unknown	Feb 11.15	N	Unknown
11716	Y	N	Unknown	Jan 28.16	N	Unknown
14464	Y	N	Harvoni	Jan 28.15	Y	Unknown
15036	Y	N	Unknown	Aug 5.15	N	Unknown
15484	Y	N	Harvoni	July 30.14	N	Dec 16.14
17502	Y	N	Unknown	Mar 18.13	N	Unknown
18447	Y	N	Unknown	Mar 9.15	Y	Unknown
18900	Y	N	Unknown	Aug 29.14	N	Unknown
19328	Y	N	Harvoni	Dec 16.14	N	Nov 20.15
19433	Y	N	Harvoni	Jan 21.16	N	Feb 2.16
19590	Y	N	Unknown	Sep 21.12	N	Unknown
20690	Y	N	Unknown	Mar 1.13	N	Unknown
20883	Y	N	Unknown	Oct 8.13	Y	Unknown
21063	Y	N	Harvoni	Apr 24.14	Y	Unknown
21185	Y	N	Unknown	Aug 27.14	Y	Unknown
21393	Y	N	Harvoni	Apr 15.15	Y	Mar 31.15
1000038	Y	Y	Ibavyr/Harvoni	Jul 15.15	N	Sep 11.15
1000137	Y	N	Harvoni	Nov 3.14	N	Dec 12.14
1000207	Y	N	Harvoni	Sep 8.14	N	Feb 2.15

Claim ID	Approved at Level 3 meets the protocol with CASL Guidelines	Was Interferon or Ribavirin taken?	Drug taken	Date Tran 2/ Hemo 2 Completed	Is there also a Fibroscan or Liver Biopsy result indicative of Non-Bridging Fibrosis?	Date of HCV Treatment
1000219	Y	Y	Pegasys/Incivek	Dec 14.12	N	Jan 23.13
1000378	Y	N	Harvoni	Dec 31.15	Y	Unknown
1000435	Y	N	Harvoni	Jul 7.15	Y	Unknown
1000507	Y	N	Simiprevier & Sofosbuvir	Aug 8.14	N	Sep 11.14
1000574	Y	N	Harvoni	Jan 2.15	N	Jun 6.15
1100027	Y	N	Harvoni	Jul 17.15	Y	Unknown
1100173	Y	N	Unknown	Jul 30.15	N	Unknown
1100287	Y	Y	Sofosbuvir/Ibavyr	Jan 23.14	N	Unknown
1100871	Y	Y	Holkira Pak	Apr 18.15	Y	Dec 16.15
1200082	Y	N	Harvoni	Feb 24.15	Y	Unknown
1200101	Y	N	Unknown	Jan 12.15	N	Unknown
1300134	Y	N	Harvoni	Mar 27.12	Y	Mar 18.15
1300255	Y	Y	Sofosbuvir/Ibavyr	Jun 15.15	Y	Unknown
1300337	Y	N	Unknown	Oct 14.15	N	Unknown
1300524	Y	Y	Pegasys/Telaprevir	Oct 16.13	N	Dec 4.13
1300818	Y	N	Harvoni	Jan 19.16	N	Unknown
1400271	Y	N	Harvoni	Dec 14.16	Y	Unknown
1400337	Y	N	Harvoni	Feb 11.14	N	Unknown
1401057	Y	N	Harvoni	Jan 21.15	N	Unknown
1401466	Y	N	Harvoni	Jan 8.15	N	Feb 10.15
1402355	Y	N	Harvoni	Jan 9.15	Y	Jan 29.15
1402639	Y	N	Unknown	Dec 1.14	N	Unknown
1402735	Y	N	Harvoni	Dec 18.14	Y	Mar 12.15
1500014	Y	N	Unknown	Jun 5.13	N	Unknown
1500027	Y	N	Unknown	Mar 25.13	N	Unknown
1500043	Y	N	Unknown	Mar 18.13	N	Unknown
1500062	Y	N	Harvoni	Sep 10.13	N	Unknown
1500094	Y	N	Unknown	Jul 23.12	N	Unknown
1500129	Y	N	Unknown	Jun 21.13	N	Unknown
1500172	Y	Y	Pegasys/Telaprevir	Feb 2.13	N	Jan 17.13