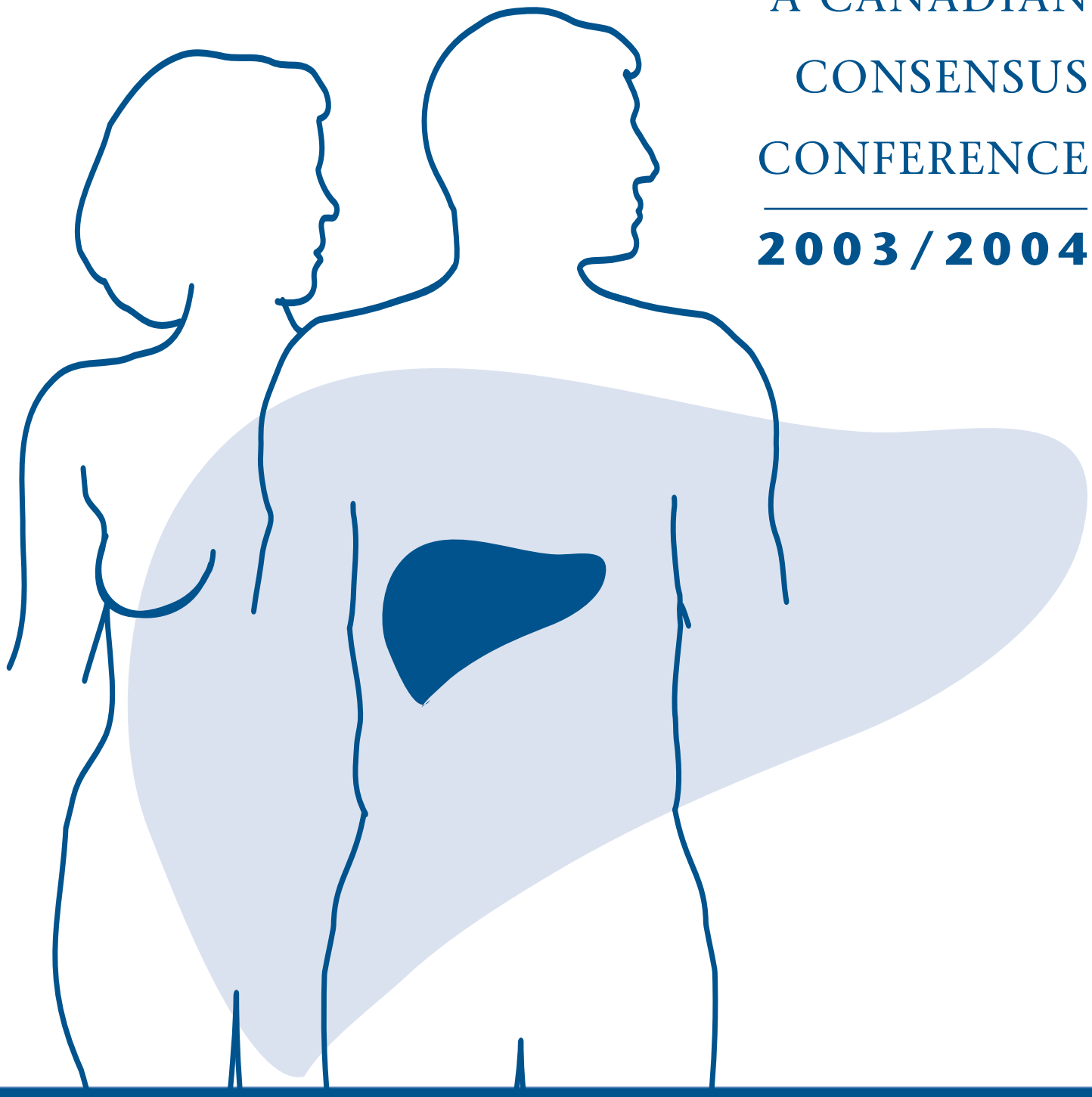
MANAGEMENT OF VIRAL HEPATITIS:

A CANADIAN CONSENSUS CONFERENCE

2003/2004



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Address for Correspondence:

Morris Sherman
Toronto General Hospital
200 Elizabeth Street
Toronto, ON
M5G 2C4

Tel: (416) 340-4756
Fax: (416) 591-2107

Email: morris.sherman@uhn.on.ca

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Prepared by:

Morris Sherman MB BCH PhD, FRCP(C), University of Toronto,

Vincent Bain MD FRCP(C), University of Alberta,

Jean-Pierre Villeneuve MD FRCP(C), University of Montreal,

Robert P. Myers MD FRCP(C), University of Calgary,

Curtis Cooper MD FRCP(C), University of Ottawa,

Steven Martin MD FRCP(C), University of Montreal,

Catherine Lowe MD FRCP(C), Queen's University.

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Members of the conference organizing committee

Canadian Association for the Study of the Liver
Dr. Winnie Wong
Dr. Vince Bain
Dr. Marc Deschênes
Dr. Sam Lee

Association of Medical Microbiology and Infectious Disease Canada
Dr. Stephen Shafran

Canadian Viral Hepatitis Network
Dr. Morris Sherman
Warren Hill PhD

British Columbia Centre for Disease Control
Dr. Mel Krajden

Canadian Association of Hepatology Nurses
Vera Simon

Correctional Service Canada
Dr. Francoise Bouchard
Josephine Muxlow

Health Canada
Dr. Tom Wong
Gregory Zaneiwski
Tracey Donaldson
Cathy Sevigny
Annie J. Lacoursière

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Preamble

Presently in Canada, an estimated 250,000 individuals are infected with the hepatitis C virus (HCV) and probably a similar number are infected with hepatitis B. The HCV-infected population is heterogeneous and includes those infected through the blood supply, through contaminated injection drug use equipment, and through use of unsterile medical equipment in foreign countries. A significant proportion of the current infections are in vulnerable populations, including persons with low incomes and unstable housing. In the future, it is anticipated that 60% to 70% of new cases will be related to substance use with 10% to 20% of these cases being co-infected with HIV and other infections. Hepatitis B in Canada, in contrast, is largely a disease of immigrant populations with up to 70% of infected individuals born in foreign countries.

There is a new appreciation of the complexities involved in managing viral hepatitis in some patient subgroups, including vulnerable populations, such as Aboriginal people, street youth, incarcerated populations, and immigrants. It is recognised that the disproportionate number of new infections anticipated in these populations in the future requires special attention to ensure adequate care. This is particularly true for patients whose health care falls under federal jurisdiction, such as Aboriginal people and inmates in the federal correctional system.

In addition to meeting the need for updated treatment information for health care professionals, this consensus conference also provided an opportunity to identify gaps in the overall management of viral hepatitis in Canada and to set the stage for future strategic direction. The effective management of individuals undergoing screening, counselling or treatment for hepatitis requires the development of a broad partnership approach. Medical treatment is an important component of the management of viral hepatitis but it represents only one element of what needs to be a comprehensive approach. In order to maximize the chances of successful therapy and minimise the long-term consequences of the disease, the root determinants of health need to be considered. The management of the patient with viral hepatitis includes, in addition to drug therapy measures, help in dealing with alcohol and other addictions, dietary management and weight reduction, and in some cases, the provision of adequate housing and nutrition. These factors provide the patient with a variety of possible treatment settings and support issues. The model of service delivery is important for some populations and can impact on health status and outcomes.

Treatment, especially for hepatitis C, is "labour intensive". This limits the number of patients an individual physician can manage. The provision of specialized nursing care will allow a larger number of patients to be treated. For this to occur, effective physician and nursing educational programs need to be developed to provide primary care providers with a basic knowledge and understanding of the wide spectrum of management issues.

In addition to addressing patient care issues, the conference also identified the importance of monitoring outcomes of prevention and care programs. There is the need for a national database to track prevention/care and hepatitis-targeted research, including social and behavioural factors that influence risky behaviour. This could be used to inform the development of comprehensive counselling guidelines and innovative models of service delivery. Analysis of the data could be used to define program and support needs for hepatitis virus-infected individuals; to guide best prevention and comprehensive care practices; and to determine the cost-effectiveness of treatment.

There is also a need for targeted social and behavioural research to determine the most effective strategies to prevent risk behaviour. Primary and secondary prevention best practices and models of care for chronic disease "self" management are required. In developing these models, the diverse and vulnerable populations affected by hepatitis need to be engaged to articulate their healthcare needs across the continuum of prevention, care and treatment.

Introduction

The management of infection by hepatitis viruses has undergone rapid change in the recent past. Several new drugs have become available. New assays have been introduced for the measurement of viral load, and new information has emerged regarding the natural history of the diseases caused by these viruses, and the response to treatment.

Since the introduction of interferon-α for the therapy of chronic viral hepatitis, the Canadian Association for Study of the Liver has sponsored a series of conferences at which local experts reviewed the available literature on the subject and issued clinical practice guidelines on the management of chronic viral hepatitis. These have been published in the Canadian Journal of Gastroenterology (1,2) and the Canadian Journal of Infectious Diseases, as well as on various Web sites. This current conference was jointly planned by the Canadian Association for Study of the Liver; the Association of Medical Microbiology and Infectious Disease Canada; Correctional Service Canada; the Canadian Association of Hepatology Nurses; the Canadian Viral Hepatitis Network; the Community Acquired Infections Division, and Blood Safety Surveillance and Health Care Acquired Infections Division of Health Canada. Funding was provided by Health Canada and Correctional Service Canada. The conference was held from November 7 to November 9, 2003, in Ottawa, Ontario. Invited presenters reviewed the literature, and presented expert opinions where literature was not available. A writing committee prepared a first draft of the recommendations and presented this draft to the audience, which included experts in the field, primary care physicians, hepatitis C community and advocacy groups, provincial and territorial ministries of health and professional associations. Pharmaceutical medical directors and representatives were invited as observers. The writing committee accepted feedback from participants, and then revised the draft to produce the final document. The document will provide levels of evidence for the statements and recommendations made according to the Infectious Diseases Society of America's quality standards (Table 1) (3). These grades are given in brackets at the end of the sentence.

The treatment of viral hepatitis is rapidly changing, and these changes need to be quickly incorporated into practice. Therefore, a significant number of studies have been referred to that have so far only been published in abstract form. The data have been presented at international meetings in all cases, and the conclusions from these abstracts are generally accepted as valid.

This consensus conference was not intended to provide an exhaustive overview of all of the complex issues involved in the management of viral hepatitis. The major intent was to address some of the changes in the medical management and treatment of chronic hepatitis B and C where the changes since the last consensus conference have been most significant. In addition to meeting the need for updated treatment information for health care professionals, this consensus conference also provided an opportunity to identify gaps in the overall management of viral hepatitis in Canada and to set the stage for future national strategic direction (see Preamble).

Following publication of the last consensus conference proceedings, the guidelines were adopted by some provincial/territorial reimbursement plans to define categories of patients who were eligible for reimbursement of treatment costs. However, the guidelines were also used to define categories of patients and forms of therapy that would be excluded from reimbursement. The result was that it became very difficult to obtain reimbursement for antiviral therapy if the patient did not meet the guideline criteria, and to obtain concomitant reimbursement for growth factor therapy, even in cases when this therapy was appropriate. This issue is particularly significant in Canada given that the high cost of hepatitis treatment is borne predominantly by governments, with a relatively small proportion covered by private insurance.

The current document is meant as a guide to therapy and does not claim to define the only way in which patients can be treated. The suitability of treatment for each patient cannot be described by this or any document. The needs of each patient should be assessed individually, and treatment costs should be reimbursed where treatment is appropriate. In addition, appropriate off-label uses of medication to

support patients with chronic viral hepatitis should be available (B)(III). Governments should establish mechanisms to allow reimbursement of such off-label uses where appropriate, but should also establish mechanisms to ensure that patients are appropriately treated when using compounds for which evidence of benefit has not been established by high levels of evidence (C)(III). One such mechanism may be to establish committees of experts who could review individual requests for reimbursement that fall outside of the guidelines.

Managing patients with chronic viral hepatitis is time and labour-intensive and cannot be adequately provided by physicians working alone. The best outcomes are obtained when patients are managed by a team, consisting at a minimum of physicians and nurses. Therefore, it is strongly recommended that there be support for training and deployment of nurses trained in hepatitis, just as there are nurses trained to manage, e.g., diabetes, cancer and to provide palliative care, and that financial support be provided for the development of hepatitis clinics.

This document deliberately does not specify particular groups of patients who should be treated or excluded from treatment. The weighing of the benefits of therapy versus the likelihood of response and of significant side effects is left to the individual physician. Thus, this document, unlike previous documents, does not exclude active injection drug users from therapy. In all cases, the decision to treat has to be individualized.

HEPATITIS B

Prevention of hepatitis B virus infection

Universal vaccination against hepatitis B is effective in preventing transmission of disease (I)(4,5). In Canada, where chronic hepatitis B infection is largely a disease of immigrants (6), some provinces offer neonatal vaccination, while others offer pre-adolescent vaccination. Since chronic hepatitis B is the largest reservoir for transmission of disease, neonatal vaccination may be preferable in provinces with a high proportion of immigrants from areas of the world highly endemic for hepatitis B. In these populations, horizontal transmission in childhood is more likely (II)(7,8).

In neonates, the use of the hepatitis B vaccine and hepatitis B immune globulin is highly effective in preventing hepatitis B transmission (I)(9,10). Furthermore, once infected, the risk of a neonate developing chronic infection is greater than 90% (II)(11,12). Therefore, screening of pregnant women in the third trimester of pregnancy for HBsAg is mandatory (A)(I). There is also Canadian economic data indicating that this is a highly cost-effective strategy (13).

Treatment of chronic hepatitis B

Initial assessment

Baseline assessment should include hepatitis B serology (HBsAg/anti-HBs, HBeAg/anti-HBe), and tests of disease activity (AST, ALT), disease severity (clinical evaluation, albumin, prothrombin, bilirubin, and complete blood count). Viral replication (quantitative HBV-DNA measurement) should be measured in patients with evidence of active disease (elevated ALT) (A)(II). Liver histology, although not mandatory, is highly recommended in patients with active disease (A)(II). Patients with mild disease may not require treatment despite active viral replication.

All hepatitis B carriers should be offered testing for anti-HIV antibodies (A)(I). Although the prevalence of HIV is low in some populations (e.g., South East Asians), the impact of monotherapy with lamivudine, adefovir or tenofovir in a patient with undiagnosed HIV infection is great due to the potential for the HIV to develop drug resistance. Anti-HCV antibodies should also be measured since HBV-HCV co-infection may impact on the selection of treatment (A)(I)(14).

Hepatitis A vaccination is recommended in patients with chronic hepatitis B (B)(II)(15,16).

Hepatitis B and hepatocellular carcinoma

Because of the increased risk of developing hepatocellular carcinoma (HCC), it is recommended that patients with chronic hepatitis B undergo regular surveillance to detect early HCC (C)(III)(17,18). However, the risk is not equal in all infected individuals. Patients with established cirrhosis are at highest risk, but patients with non-cirrhotic liver disease may also be at risk. Patients who have been documented as having inactive disease for many years and who are not cirrhotic (usually anti-HBe-positive and usually Caucasian) are at much lower risk (A)(II)(19,20). Such patients may not require surveillance.

Although there is no evidence that surveillance for HCC reduces disease-specific or all-cause mortality, surveillance with abdominal ultrasound and serum alphafetoprotein every six months is common practice. However, what little evidence exists suggests that annual surveillance is just as effective (21,22).

Who should be treated?

Acute hepatitis B infection does not require antiviral therapy (B)(III).

Hepatitis B-infected individuals, whether HBeAg-positive or HBe-negative with elevated AST and/or ALT, and HBV DNA >100,000 copies/ml are candidates for therapy (A)(I). When the HBV DNA <100,000 copies/ml, the likelihood of hepatitis B-induced injury is thought to be low (23). The distinction between HBeAg-positive and negative patients may impact on the choice and duration of therapy. The decision to treat or not may also be influenced by the severity of disease on liver biopsy.

Observation without treatment is appropriate in patients with mild disease. However, such patients should be followed at close intervals.

How to assess response to treatment?

Response to treatment can be defined virologically or biochemically. A complete virological response is defined as the sustained loss of HBsAg after treatment, but this occurs only rarely (I)(24). In HBeAg-positive carriers, a partial virological response is defined as the sustained loss of HBeAg with gain of anti-HBe after treatment (HBeAg seroconversion)(25). An alternate endpoint for a partial virological response is a decrease in serum HBV-DNA below 100,000 copies/ml (26). A biochemical response is defined as a normalization of serum AST and ALT. Liver biopsy is not mandatory to assess treatment efficacy (B)(II)(26). Response is initially assessed while on therapy (on-treatment response). For patients treated with time-limited regimens (e.g., interferon), response is also assessed after completion of therapy. The optimal time post therapy for assessing this response has not been defined.

The utility of determining HBV genotype needs to be explored, as it may impact on treatment efficacy.

What treatment should be used?

Lamivudine or interferon are both acceptable as initial treatment (A)(I).

Interferon in HBeAg-positive patients

Treatment should be with 10 million international units (MIU) interferon alpha subcutaneously (sc) three times per week (TIW) or 5 MIU sc daily for 16 weeks (I)(26,28-32). Some believe that longer duration therapy (up to 24 weeks) may be justified in selected cases (27), such as those with high viral loads (>10^8 copies/ml). A partial virological response (HBeAg seroconversion) may be expected in 25-40% of patients six months after completion of therapy. Response rates are decreased in the presence of high viral loads (>10^8 copies/ml), mild hepatic inflammation (AST or ALT <1.5 times the upper limit of normal [xULN]), age over 40 years, presence of cirrhosis and male gender.

The durability of HBeAg seroconversion after interferon treatment in Caucasian populations is high (68% three years after stopping therapy) (II)(33). However, in other populations (e.g., South East Asian), the durability of seroconversion may be lower (III)(34,35).

In Caucasian populations, interferon therapy has been shown to enhance overall survival and complication-free survival in HBeAg-positive patients who maintain post-treatment seroconversion (II)(36). The effect of interferon therapy on survival in Asian populations may not be as pronounced (35,37).

Interferon may be more appropriate than lamivudine as initial treatment in young patients, particularly in the absence of cirrhosis, but there is no consensus on this issue. One rationale is that it may be preferable to use a time-limited form of therapy in a young patient who might otherwise have to be on therapy for many years, and who can tolerate the side effects of interferon.

Interferon in HBeAg-negative patients

The recommended dosage of interferon is 5-10 MIU TIW sc for one to two years. The response rate is lower than for HBeAg-positive patients, and the durability of response is also less well established (II)(38-40).

Lamivudine in HBeAg-positive patients

The recommended dosage is 100 mg p.o. daily for up to five years or more, until a partial virological response (HBeAg seroconversion) occurs, or until lamivudine resistance develops (I)(41-43). A partial virological response (HBeAg seroconversion) can be expected in 18-25% of patients within the first year of therapy, rising to about 60% after three years of therapy.

The durability of HBeAg seroconversion after lamivudine is not as good as after interferon therapy. Continuing treatment for six months after seroconversion may improve the durability of seroconversion (II)(44).

There are several areas of uncertainty concerning lamivudine resistance. Phenotypic resistance is defined as the reappearance of HBV DNA following initial disappearance using a non-PCR-based assay, or by a rise in HBV DNA concentration to >100,000 copies/ml in a PCR assay. Genotypic resistance refers to the demonstration of mutations in the YMDD motif of the HBV polymerase gene. Patients with

phenotypic resistance have a 97% probability of having genotypic resistance (45) and therefore, the utility of confirming phenotypic resistance by genotyping is unclear. Once resistance occurs (approximately 60% after four years of therapy) (46), it is unclear whether lamivudine should be withdrawn. Disease severity does appear to progress once resistance develops (46,47), but it is uncertain whether the rate of progression is slower than in the absence of lamivudine. HBeAg seroconversion has also been reported after the development of lamivudine resistance (46). There is also a concern that lamivudine withdrawal may precipitate a flare of hepatitis, which could be fatal in patients who have underlying cirrhosis. However, the evidence supporting this is only anecdotal. No recommendation can be made regarding whether lamivudine should be withdrawn or not once lamivudine resistance develops. Once resistance has developed, patients can be offered treatment with interferon (if they have not previously failed interferon) or adefovir dipivoxil (see below).

Lamivudine in HBeAg-negative patients

In HBeAg-negative patients, lamivudine is used at the same dosage (100 mg PO daily) (I)(48-50). The optimal duration of treatment is uncertain. For patients with a biochemical and virological response (i.e., normal AST, ALT, and HBV-DNA <100,000 copies/ml) on therapy, there are no guidelines as to when treatment should be stopped. In patients in whom treatment is stopped after one year, the relapse rate is high, and possibly no more than about 13% of patients remain in remission. Possible endpoints for stopping treatment might be negative HBV DNA by PCR or negative HBcAg on liver biopsy. Similarly, it is unclear whether treatment should be stopped or continued once lamivudine resistance develops. However, as in patients with HBeAg-positive chronic hepatitis B, the options to use interferon or adefovir remain.

Adefovir dipivoxil

Adefovir dipivoxil is a new nucleotide analogue that is effective in both treatment-naïve and lamivudine-resistant HBV infection (I)(51,52) that will soon be available in Canada. Although initially studied as first-line therapy for chronic hepatitis B, its role as first-line treatment in patients remains unclear. It seems to be less effective than lamivudine in inducing HBeAg seroconversion, and may also be less potent in inducing viral suppression. Its use as a first line drug may also be limited because of cost considerations. It is indicated for therapy of lamivudine-resistant infection and in patients who have failed to respond to lamivudine initially and who do not tolerate or have failed interferon (53). As adefovir is a new therapy, there are still several areas of uncertainty. Renal toxicity can occur in some cases and dose adjustments are required for patients with established renal disease. The rate of development of resistance to adefovir appears to be much lower than with lamivudine (54), but experience is limited. The durability of seroconversion in HBeAg-positive patients remains unknown. As with all forms of hepatitis B therapy, flares of hepatitis can occur after cessation of therapy. Combination therapy with adefovir and lamivudine to limit the development of resistance (by analogy with HIV-positive patients) needs to be explored.

Pegylated interferon

The efficacy of pegylated interferon in the treatment of HBV infection is being investigated, but the available data are too limited to allow specific recommendations to be made. Preliminary data suggest that the efficacy of pegylated interferon is at least comparable to that of standard interferon (55).

Special situations

Hepatitis B in children

The principal goals of therapy of hepatitis B in children are to reduce horizontal transmission of infection as well as to minimize long-term disease-associated morbidity. The decision to treat a child must take into account that there is a significant rate of spontaneous seroconversion in childhood, which differs in different populations. In Mediterranean and Alaskan populations, 8-16% of children per year will undergo HBeAg seroconversion (56,57). In Asian children with normal ALT, the rate may be 2-5% per year and 11% per year in those with elevated ALT (58,59). Thus, by twenty years of age, as many as 80% of children will undergo spontaneous HBeAg seroconversion in regions of low or moderate endemicity and 25-70% in regions of high endemicity (57,59,60). Predictors

of spontaneous seroconversion include ALT >3 xULN, high histological activity index, female gender and low HBV-DNA (i.e., the same predictors of treatment response). Clinical trials of treatment with interferon or lamivudine provided insufficient follow-up of control groups. Other studies have shown that, by three years of follow-up, treated and controlled patients have the same rates of seroconversion (59,60), suggesting that treatment mainly accelerates seroconversion by about three years. The long-term benefits of a three-year seroconversion advantage afforded by treatment have not been established. Cirrhosis and HCC are rare in children (usually <5%); and, in adolescents, do not always present after a long period of inflammatory activity. Cirrhosis is well described in young children with short duration disease. Similarly, children who get HCC usually achieve HBeAg seroconversion in the first few years of life.

Interferon-α 6MIU/m^2 sc (maximum 10MIU) TIW for 24 weeks has been approved for children with HBeAg-positive hepatitis B. This will achieve a partial virological response in approximately 35% (I)(61). Lamivudine, 3 mg/kg/day (maximum 100 mg) for one year has also been approved, with partial virological (HBeAg seroconversion) response rates of 23% but with the development of lamivudine resistance in 19% (I)(62). Therefore, treatment may be appropriate in HBeAg-positive adolescents who have failed to undergo spontaneous HBeAg-seroconversion despite ALT >2x ULN for 6-12 months. In younger patients, moderate or severe inflammation on liver biopsy may also justify treatment (III). Lamivudine may be more appropriate for younger patients due to its ease of administration and better side effects profile. Interferon may be more suitable in some older children in whom short-term therapy and monitoring may be required. Regardless of type of therapy, all children should continue to be followed at one to two-year intervals to monitor for durability of response (III). Children should also be entered into long-term monitoring programs, to detect complications such as HCC (III).

Pregnant women

Some recommend the use of lamivudine in pregnant women with high HBV DNA levels to reduce the risk of neonatal transmission (III)(63). To date, there are no reports of fetal injuries due to lamivudine. A single study has shown that if the HBV DNA levels are very high (>10^9 copies/ml), the rate of maternal-fetal transmission is approximately 30% despite neonatal vaccination (63).

Decompensated cirrhosis

Interferon is contraindicated in these patients. Lamivudine is the first choice in patients with active viral replication (HBV DNA >100,000 copies/ml) (I)(64,65). Lamivudine may reduce or delay the need for liver transplantation in these patients. In contrast, the benefit of lamivudine in patients with advanced cirrhosis and inactive or low-level viral replication (<100,000 copies/ml) is doubtful, and lamivudine should not be used under these circumstances (B)(III).

HBV-HCV co-infection

Some favour the use of interferon, as it may be effective in both infections (III). The most appropriate way of combining interferon and ribavirin has not been established. However, no firm recommendations can be made regarding the use of interferon vs. lamivudine.

Renal transplant candidates

Lamivudine treatment is recommended in all HBsAg-positive patients prior to and following kidney transplant to avoid HBV reactivation following immunosuppression after transplantation (II)(66). Whether lamivudine should be used in patients with markers of past HBV infection (anti-HBs-positive and/or anti-HBc-positive) to prevent reactivation is not clear, although HBsAg should be monitored to detect reactivation. Similar considerations apply in other circumstances where immunosuppressive therapy is used for immunologically-mediated diseases.

Chemotherapy and bone marrow transplant (BMT)

All patients undergoing chemotherapy or BMT should be screened for HBV markers prior to treatment (B)(II). In those who are positive for HBsAg, preemptive lamivudine treatment should be used to prevent flares of HBV that can occur with these treatments (II)(67). Since flares of hepatitis

occur mostly as a result of immune recovery, treatment with lamivudine can be started a few days before starting immunosuppressive therapy. There is no information to guide how long patients should be treated. For patients in whom immunosuppression continues (e.g., after BMT), lamivudine therapy should also continue. However, once all courses of chemotherapy have been completed, lamivudine can be withdrawn (C). Some suggest a period of maintenance therapy of a few months after chemotherapy before withdrawal (C). Whether subjects with markers of past HBV infection should also be treated is unclear. Chronic HBV infection in the BMT recipient can be cured by adoptive transfer of immunity from a bone marrow donor with evidence of past hepatitis B infection (II)(68). In BMT recipients who are HBsAg-positive, the bone marrow donor should be screened for markers of HBV infection to determine whether adoptive transfer of immunity would be a possibility (II).

HIV-HBV Co-infection

Lamivudine should never be used as monotherapy for HBV infection in untreated HIV patients as the rapid development of HIV resistance to lamivudine may jeopardize future treatment in these cases (II). Adefovir and tenofovir, another nucleotide analogue developed to treat HIV that is effective against both wild-type and lamivudine-resistant HBV strains, should also not be used as monotherapy for HBV-HIV co-infected patients (II).

The prevalence of HBV-HIV co-infection is approximately 5% but variable depending on location (69). HBV is more active and liver fibrosis is often more advanced in HBV-HIV co-infection compared to HBV infection alone (70,71). Anti-HBs and HBsAg screening should be performed in all HIV sero-positive individuals (A)(II). Vaccination is recommended for those negative for HBsAg and anti-HBs. Because the HIV population in general is hypo-responsive to hepatitis B vaccination, either a schedule using a double dose (72), or six standard doses (73), is advised (A)(II). Hepatitis A virus vaccination is also recommended (B)(II)(74,75). A multidisciplinary approach for the delivery of care is ideal for the management of HIV-HBV co-infection, including specialists in infectious diseases and hepatology or gastroenterology (C)(III).

In the case of HIV-HBV co-infection, highly active antiretroviral therapy (HAART) regimens containing the reverse transcriptase inhibitors (NRTI) lamivudine and/or tenofovir are ideal given that these drugs possess virologic activity against both HIV and HBV and infrequently cause hepatotoxicity (B)(II)(76).

Adefovir should not be used because the dose used to treat hepatitis B (10 mg/day) is inadequate to control HIV, and the doses appropriate for HIV are associated with significant toxicity. Furthermore, there is cross-resistance between adefovir and tenofovir. Tenofovir is preferred to adefovir in the HBV-HIV co-infected patient. The rates of aminotransferase normalization, reduction in HBV DNA to undetectable levels, loss of HBeAg and development of anti-HBe are comparable between interferon, lamivudine, and tenofovir (77-79). An advantage of tenofovir over lamivudine may be the slower evolution of drug resistance and the efficacy of tenofovir in HBV-infected individuals with lamivudine-resistant HBV (79,80).

There are patients who require therapy for their hepatitis B, but who would not otherwise qualify for HAART. Since nucleoside analogue monotherapy is not acceptable, these patients may need to go onto HAART, simply to allow control of their hepatitis B (C)(III). Alternatively, interferon could be used.

There are additional treatment issues around hepatitis B that were not addressed in this conference. These include the management of hepatitis D, the prevention and treatment of hepatitis B infection in liver transplant recipients, and the treatment of hepatitis B in hemodialysis patients.

Hepatitis C

Initial Assessment

Initial evaluation of suspected hepatitis C infection involves serologic testing for antibodies against hepatitis C (3rd generation enzyme-linked immunoassay [EIA]). Testing for hepatitis C should be undertaken in all patients with abnormal aminotransferase levels and in those with risk factors for hepatitis C infection (A)(II). These include prior injection drug use, even if remote and only occasional, transfusion of blood products prior to 1990, and immigrants from countries with high prevalence rates of hepatitis C. In many countries from which Canada draws immigrants, large numbers of patients were infected with hepatitis C 30-50 years ago, related to medical procedures using improperly sterilized syringes and needles (81,82,127).

The initial evaluation should also include a careful review of the patient's history to exclude contraindications to therapy and identify areas that need attention during treatment. Particular attention should be paid to a previous or current history of psychiatric disorders, seizure disorders, cardiac and renal disease, autoimmune disease, alcohol and drug addiction, retinopathy, and the presence of co-infections such as hepatitis B and HIV. Contraindications to antiviral treatment for hepatitis C are listed in Table 2 (B)(II).

In anti-HCV-positive patients, infection should be confirmed with a highly sensitive qualitative HCV RNA assay (A)(II). It is impossible to treat hepatitis C properly without viral load and genotype testing. Therefore, viral load and genotype testing has to be available in a timely fashion (A)(I). These assays are essential to the proper management of patients and are cost efficient, in that they allow early termination of costly therapies where appropriate.

Laboratory assessment prior to treatment should include genotype, HCV RNA levels where appropriate (see later), CBC, PT, INR, albumin, AST, ALT, bilirubin, alkaline phosphatase, HBsAg, HIV, TSH, ANA, glucose, creatinine, serum or urine β-HCG (to exclude pregnancy) and urinalysis (B)(II). Additional tests include abdominal ultrasound and ECG (if age over 50 or history of cardiac disease) (B)(II). Liver biopsy remains the most sensitive measure of disease severity and is recommended but is not mandatory prior to the initiation of therapy (B)(II). Patients with genotype 2 and 3 infection, who have a high likelihood of cure, may not need a liver biopsy prior to treatment (B)(I).

Sexually-active females must have a pregnancy test prior to initiation of therapy, because of the teratogenicity of ribavirin (B). Because urinary pregnancy testing has limited sensitivity and can result in false negative readings, serologic testing is preferred. Sexually-active patients, male or female, must agree to use a highly effective method of contraception during therapy and for six months following completion of therapy for the same reasons.

Choosing patients for antiviral therapy

With recent improvements in sustained virological response (SVR) using combination treatment with pegylated interferon and ribavirin, all patients, no matter what the apparent state of their liver disease, should undergo evaluation to determine whether therapy is appropriate (A)(I). This recommendation is different than previous recommendations. The decision to treat or not to treat is complex and must consider factors such as the risk for liver disease progression, likelihood of treatment response, risk of adverse effects, patient symptoms, and of course, the patient's wishes. Although some have advocated the selective treatment of only those patients with advanced fibrosis or severe inflammation on liver biopsy, the large registration trials that have been published included a significant proportion of patients with mild inflammation and/or fibrosis. Patients with mild disease, especially minimal fibrosis, have the best response to therapy. Therefore, the exclusion of this group from treatment would lead to overall SVR rates that are inferior to usually quoted values. Second, simply because a patient has not been infected long enough to develop significant liver injury is not a reason to withhold treatment. However, for patients with mild hepatitis, the possibility of declining treatment with the hope of future advances in antiviral therapy should be discussed.

The primary endpoint of therapy is an SVR, defined as a negative serum HCV RNA by a qualitative test sensitive to <50 IU/ml six months after the completion of therapy (83,84). Studies have indicated that patients who achieve this outcome no

longer have detectable HCV RNA in the liver, and do not relapse in the ensuing years (85). For practical purposes, a sustained virological response is equivalent to a cure with less than 2% suffering a late relapse (I)(85).

Drug treatment

The best results have been obtained using a combination of pegylated interferon and ribavirin (A)(I)(86,87). Viral genotype has the most profound influence on the likelihood of treatment response. Manns et al. (86) have reported an SVR of 42% in genotype 1 patients using peginterferon alpha-2b at a dose of 1.5 μg/kg sc weekly, together with ribavirin 800 mg daily for 48 weeks. This was superior to combination treatment using standard interferon and ribavirin (SVR 33% in genotype 1). In retrospect, the ribavirin dose used in this study was likely too low. Subsequent studies have suggested that 1000-1200 mg PO is a more suitable dose for genotype 1, depending on whether the patient is less than or heavier than 75 kg (I)(88). Fried et al. (87) have reported a similar SVR of 44% in genotype 1 patients using peginterferon alpha-2a at a dose of 180 μg sc per week plus ribavirin, 1000-1200 mg PO daily. The initial registration studies for pegylated interferon/ribavirin did not distinguish between genotype 1 and genotypes 4, 5, or 6. Therefore, current practice is to treat genotypes 4, 5, and 6 as genotype 1 until more data are available (B)(II).

Genotype 2 and 3 infection is optimally treated with a 24-week regime using peginterferon alpha-2a, 180-μg sc weekly or peginterferon alpha-2b, 1.5 μg/kg sc (I). A fixed dose of 800 mg ribavirin PO daily is sufficient when using either pegylated interferon-α, 2a, or 2b (A)(84,86). SVRs of 78-82% may be achieved.

The other major factor influencing the SVR is viral load, with better results being observed in patients with lower viral loads (e.g., less than about 800,000 IU/ml)(86-88).

There are currently two preparations of pegylated interferon. At the time of writing, only one is available in Canada. The second preparation is expected in 2004. Both manufacturers have chosen to bundle the interferon and ribavirin, so that a fixed ribavirin dose is provided with each dose of interferon. This so-called bundling only occurs in Canada. In the USA and in Europe, the two drugs, pegylated interferon and ribavirin are available separately. While there are advantages to bundling, the major drawback is a loss of flexibility to tailor the ribavirin dose as required. The consensus conference speakers and attendees strongly recommend to the manufacturers that the two products be available in an unbundled form.

There are no direct comparisons of the efficacy of peginterferon alpha-2a and peginterferon alpha-2b. Given the uncertainties of comparing outcomes from separate trials, no conclusions can be reached regarding the superiority of one agent over the other. The large trials differed with respect to the proportion of patients with genotype 1, mean body weight and proportion with advanced fibrosis (METAVIR stage F3 or F4) (86,87,89). Furthermore, although the adverse effect profiles seem comparable, different adverse event definitions were used, so that direct comparisons of the side effect profiles are not possible.

Early virological response (EVR)

For patients infected with genotype 1, the likelihood that an individual patient will not have an SVR can be reliably predicted after 12 weeks of therapy by assessing the EVR (I). EVR was defined in the registration studies as either undetectable HCV RNA or at least a 2-log drop in HCV-RNA concentration. Patients failing to achieve an EVR have only a 0-3% chance of achieving an SVR. Therapy should therefore be stopped for these patients (A)(I)(87,90). Those achieving an EVR have a 65-72% chance of achieving an SVR. Quantitative HCV RNA assays have an inherent variability that might be as high as 0.5 logs. Therefore, the EVR rule cannot be applied too strictly. Therapy should be stopped for patients who fail to achieve EVR. However, EVR should be defined as failure to achieve a decline in HCV RNA of 1.8 log compared to baseline at 12 weeks of therapy (B)(III). Patients who achieve a 1.8 or 2-log drop, but who do not clear HCV RNA from serum at week 12 should be tested with a qualitative HCV RNA at 24 weeks (C)(III). Those who fail to clear the virus at 24 weeks should have therapy withdrawn, as they are extremely unlikely to achieve SVR (A)(I)(88,90). Although these predictive rules were devised for genotype 1 patients, there are preliminary data that suggest that the EVR rule is useful in genotype 4 patients as well (91).

Patients infected with genotype 2 and 3 achieve EVR in 97% of cases. There is therefore no merit to measuring HCV RNA at 12 weeks in this group.

All patients who complete a course of therapy should have HCV RNA measured at the end of therapy to define the nature of their treatment response (C)(III). Some patients will achieve EVR, but develop breakthrough viremia before the end of therapy. It may be important, when considering future therapy, whether a patient was a non-responder to interferon and relapsed during or after treatment.

Evaluation and monitoring during treatment

Treatment of hepatitis C has numerous side effects that can be severe, life threatening, and irreversible. Therefore, patients must be evaluated carefully and monitored vigilantly during and after treatment.

Laboratory assessments include CBC at week 1, 2, 4, 6, 8, and then monthly. ALT, bilirubin, glucose, and urinalysis should be done monthly, TSH and weight every three months (B)(I)(92,93). Pregnancy tests must be done regularly. The common laboratory abnormalities requiring intervention are anemia and neutropenia. The manufacturers recommend that dose reduction of ribavirin is required for hemoglobin levels below 100 g/L, and discontinuation is required if the hemoglobin level falls below 85 g/L (94,95). The manufacturers also suggest that if the neutrophil count falls below 0.8 $x10^9$/L, the dose of interferon should be reduced. However, studies suggest that even at neutrophil counts of $0.5x10^9$/L, infection is rare (96). The effect of dose reduction on SVR has not been fully evaluated. As long as patients receive more than 80% of the intended dose of all therapy, the reduction in SVR rates is small (87,97). For patients receiving less than 80% of the intended dose, but who continue on therapy, the SVR rate drops, but remains acceptable. Patients who prematurely withdraw from therapy have very low SVR rates. For patients with ribavirin-induced anemia, erythropoietin can be used to maintain hemoglobin concentration (98). Studies show that the use of erythropoietin allows the ribavirin dose to be maintained. As yet however, there are no data on the effect that this might have on SVR rates. GM-CSF and G-CSF have been used to treat interferon-induced neutropenia. The use of erythropoietin and GM-CSF or G-CSF are controversial, and add significant expenses, but might be appropriate in some patients (99-101).

Special situations

Normal ALT

Approximately 30% of HCV patients have persistently normal ALT (at least three normal ALT values when measured over a period of several months) (102-104). Although the majority of these patients have mild disease on biopsy, a few may have significant fibrosis (105-109). Treatment with pegylated interferon and ribavirin results in equivalent SVR rates in patients with normal ALT, compared to patients with abnormal ALT (110). Therefore, patients with persistently normal ALT should be considered for therapy (A)(I). A liver biopsy is helpful to determine those with significant disease who would benefit from treatment and will identify patients with mild disease, who might prefer to wait for newer therapies to be developed. In addition, other factors such as favourable genotype, infectivity concerns, severe symptoms, extrahepatic disease, and occupational concerns should be considered in the decision to treat patients with normal ALT.

Cytopenias

Interferon and ribavirin therapy induces declines in red blood cells, white blood cells and platelet counts. In the past, patients whose baseline levels of red and white cells and platelets in blood were low were excluded from therapy. This included patients with thalassemia and constitutional neutropenia (common in Blacks) (96). These patients should no longer be automatically refused treatment (C)(II). Unacceptable declines in cell counts during therapy may respond to growth factor therapy (see above).

Acute hepatitis C

Acute hepatitis C is rarely identified since the majority of patients are asymptomatic during the initial stage of infection. Since some patients may present prior to the development of anti-HCV antibodies, the diagnosis requires the demonstration of HCV RNA in serum (111). Approximately 40-50% of symptomatic patients (e.g. those with jaundice,

nausea, vomiting, right upper quadrant discomfort, flu-like symptoms) will clear the virus spontaneously (112,113). In order to avoid the unnecessary treatment of such patients, therapy should be deferred until three to four months following presentation if persistent HCV RNA positivity is demonstrated (B)(II)(114). In asymptomatic patients, immediate treatment can be considered due to the low probability of spontaneous viral clearance (113) and high rates of successful treatment when administered during the early period of infection (II)(114). Although data from randomized controlled trials are lacking, the highest rate of sustained virologic response (98%) has been reported with high dose induction therapy with standard interferon monotherapy (5 million units (MU) sc daily for 4 weeks followed by 5 MU sc TIW for 20 weeks)(B)(II)(114). However, a large proportion of these patients were symptomatic so the efficacy of therapy in asymptomatic patients is unclear. The efficacy of combination therapy with ribavirin and the role of peginterferon alpha has yet to be established, but may well be necessary in asymptomatic patients.

Cirrhosis

Although the majority of patients with chronic hepatitis C have mild disease, a significant proportion will progress to cirrhosis. The majority of the complications of chronic hepatitis C including liver failure, variceal bleeding, and hepatocellular carcinoma, occur exclusively in these patients (115). Therefore, cirrhotic patients have the most to gain from successful antiviral therapy. Unfortunately, rates of sustained virologic response are lower and tolerance is generally poorer in patients with advanced disease. Treatment of patients with decompensated cirrhosis with interferon-based regimens is contraindicated outside specialized care environments due to the risk of precipitating severe liver failure and potential death (B)(II)(116). In patients with compensated cirrhosis, the optimal therapy is the combination of peginterferon and ribavirin (B)(II). Subgroup analyses of the large registration trials of this therapy revealed rates of sustained virologic response of 43-44% (in patients with bridging fibrosis and cirrhosis combined) (86,87). The dosage and duration of therapy should be the same as in non-cirrhotic patients; however, dosage reductions may be necessary in patients with pre-existing cytopenias. Adjunctive therapy with growth factors including erythropoeitin and G-CSF may be useful in these patients, but data are limited. The role of maintenance interferon-based therapy is under study and cannot currently be recommended (D)(III).

Extrahepatic manifestations of hepatitis C

There are several conditions related to hepatitis C that might require therapy, even in the absence of significant liver disease. These include cryoglobulinemia and glomerulonephritis. However, the treatment of these conditions has not been standardized. Neither the dose nor duration of therapy has been determined. Therefore, no recommendations can be made about how to treat these patients. However, such patients are probably best treated in specialized centres.

Re-treatment of Patients

Selected patients who have failed to respond to interferon-based therapy should be considered for re-treatment. The decision to re-treat patients should consider the previous therapy received, the tolerance of and response to prior treatment (non-response versus relapse), and factors predictive of an SVR. Patients with advanced fibrosis (stage 2 or greater) should be given priority for re-treatment (C)(II). "Relapsers" become HCV RNA-negative during treatment (as manifested by an EVR or end-of-treatment virologic response), but have reappearance of HCV RNA following the withdrawal of therapy. "Non-responders" fail to achieve HCV RNA negativity during treatment. The latter group is more resistant to re-treatment with interferon-based regimens. In patients with a relatively good likelihood of response who have relapsed or not responded to interferon monotherapy, combination therapy with peginterferon alpha and ribavirin at standard dosages and duration is the preferred re-treatment strategy (B)(II). In relapsers and non-responders to interferon and ribavirin combination therapy, re-treatment with peginterferon alpha and ribavirin can be considered, although efficacy data from randomized controlled trials are not currently available (III). Preliminary data suggest that about 10% of non-responders and about 20% of relapsers achieve an SVR (117,118). The optimal dose and

duration of therapy has yet to be identified, although patients should receive at least the minimum therapy recommended for treatment-naïve patients.

Renal impairment and renal transplantation

Peginterferon alpha-2b is relatively contraindicated in patients with a creatinine clearance below 50 mL/min because peginterferon alpha-2b is excreted by the kidney (94). Peginterferon alpha-2a can be administered at full dosage (180 μg/week) in patients with a creatinine clearance above 20 mL/min, and a reduced dosage (135 μg/week) in those with more severe renal dysfunction (95). Ribavirin is contraindicated in patients with significant renal dysfunction (creatinine clearance <50 mL/min) due to altered pharmacokinetics and the risk of severe anaemia. Ribavirin has been used, however, in specialized care centres at low dosages with therapeutic monitoring of plasma ribavirin concentration (119). In patients with previous renal transplantation, interferon is contraindicated due to the risk of precipitating irreversible graft dysfunction (II)(121)(120,122).

Children with chronic hepatitis C

Although the progression of chronic hepatitis C appears slower in children than adults (121), some children have significant fibrosis on liver biopsy (II). These findings suggest that antiviral treatment may be warranted in selected patients; however, the indications for therapy are poorly defined. As in adults, the decision for treatment must consider the efficacy and adverse effects of therapy and the severity of the underlying liver disease. Children with hepatitis C are typically asymptomatic and the majority have normal or minimally-elevated serum aminotransferases (II)(122). Since the correlation between ALT and hepatic histologic lesions is poor, a liver biopsy should be considered in the management of infected children, particularly after ten years of infection (C)(III). Patients with moderate to severe fibrosis and/or necroinflammatory activity on liver biopsy should be targeted for therapy, preferably at specialized centres (C)(III). Standard interferon (3 MU/m^2 three times weekly) and ribavirin (15 mg/kg/day) for 48 weeks yields rates of sustained virologic response similar to that observed in adults (40-60% overall, 70-100% in genotypes 2 and 3) (II)(123,124). The efficacy of peginterferon and ribavirin has yet to be conclusively demonstrated. Interferon is generally well-tolerated in children, with weight loss being the only side effect presenting more frequently than in adults. The resultant growth inhibition is not permanent (125). Children under three years of age should not be treated due to concerns regarding the potential neurotoxicity of interferon on the developing brain (126) and the higher rates of spontaneous viral clearance observed in this subgroup.

HIV-HCV co-infection

Approximately one-quarter of Canadian HIV-infected individuals are seropositive for HCV (127). Among HIV seropositive injection drug users, this rate is at least 50% and up to 80% in some regions (128). Since the introduction of HAART liver disease secondary to HCV infection has become a leading cause of morbidity and mortality in HIV-HCV co-infection (129). Progression to cirrhosis and decompensated liver disease is accelerated in HIV-HCV co-infected patients (130-132). Immunodeficiency (CD4 <200 cells/ml) and excess alcohol consumption (>50 grams per day) are independently associated with rapid progression to cirrhosis. The influence of HCV on HIV infection is less pronounced (133,134). CD4 T cell recovery following initiation of HAART may be blunted in comparison to HCV sero-negative individuals with HIV (135,136). Mildly-elevated aminotransferases, biopsy inflammation scores, and liver fibrosis may be improved in HIV-HCV co-infected subjects receiving potent and durable HAART, compared to baseline (137,138).

Screening and investigations

HCV screening by serology is recommended in all HIV-infected individuals (B)(II). HCV RNA testing by PCR should be done in the setting of patients who are anti-HCV negative but at high risk of HCV, i.e., patients with abnormal liver enzymes in the absence of other causes of liver disease or patients with high risk for acquiring HCV infection. Liver biopsies in HIV-HCV co-infection identify at least some disease activity in most patients (> 95%)(139). In one study, three quarters of HIV-HCV co-infected subjects were found to have METAVIR stage 2 or 3 fibrosis and 10% were cirrhotic. A biopsy is strongly recommended to stage fibrosis, assist in the decision regarding the need

for drug therapy, predict the likelihood of response to therapy, and identify cirrhotics who may be at more risk of treatment-related hepatotoxicity (A)(II).

Treatment environment

The management of HIV-HCV co-infection is more complex than management of either disease alone. Therefore, a coordinated multidisciplinary approach for the delivery of care is strongly recommended (C)(II).

Hepatitis C drug therapy

A decision to initiate therapy should be based on similar criteria to that used in HCV mono-infected individuals (A)(I). Because HCV progresses more rapidly in HIV-HCV co-infected patients, treatment may be considered in those with minimal fibrosis (i.e., stage 1) and/or normal ALT (C)(II).

The SVR rate with 48 weeks of pegylated interferon alpha-2 plus ribavirin for genotype 1 infection is under 30% (I)(139-143). The SVR rate with 48 weeks treatment for genotype 2 and 3 infection may be as high as 62% with low virological relapse rates between end of therapy to 72-week follow-up (I)(140,141). It is unclear if 24 weeks of therapy is sufficient, as a 29% relapse rate has been reported after the end of therapy for genotype 3 infection (139). The early virologic response, defined as at least a 2-log drop in HCV viral load, should be determined as lack of an early virologic response predicts failure to achieve SVR (A)(I). Given the low rates of SVR, HCV therapy should be initiated using the full recommended doses of interferon and ribavirin with aggressive supportive therapy for drug-induced side effects as SVR rates are reduced with sub-therapeutic dosing in HCV mono-infected patients (B)(II).

The constitutional and cognitive toxicities related to therapy are significant (143), but in general, are not more frequent or severe in comparison to those infected with HCV alone. Therapy in this population is often contraindicated because of co-morbid illnesses such as psychiatric illness, severe cytopenias, and uncontrolled substance abuse. Severe adverse interactions between antiretrovirals and HCV drug therapy occur rarely and can usually be prevented by careful laboratory monitoring and avoiding combinations of certain medications. Caution should be exercised when didanosine and ribavirin are used in combination because of the risk of mitochondrial toxicity (lactic acidosis and pancreatitis) (I)(144-146). As both zidovudine and ribavirin can cause anemia, careful attention is warranted if co-administered (C)(II)(147). Although ribavirin may alter the intracellular levels of several nucleoside reverse transcriptase inhibitors (NRTI)(148), neither increased treatment side effects nor loss of HIV virologic suppression have been reported in NRTI-treated subjects initiating ribavirin.

Use of antiretrovirals

There is a risk of hepatotoxicity with antiretroviral therapy (149,150). Hepatic steatosis and fulminant hepatitis are rare complications of HIV NRTI treatment (150-154). These toxicities are mediated by NRTI inhibition of mitochondrial DNA replication (151). Severe elevation of aminotransferases (defined as >10x the upper limit of normal) occurs in between 5-10% of patients, for most protease inhibitors (152-154), are usually asymptomatic and resolve without interruption of antiretroviral therapy. However, the patient should be monitored closely for signs of liver failure. A 2-4% incidence of rise in aminotransferases is reported in treatment-naïve subjects receiving non-nucleosidase reverse transcriptase inhibitors (151). An early nevirapine hypersensitivity syndrome consisting of fever, rash, and elevated ALT has also been described but is observed infrequently (154,155). Treatment limiting hepatotoxicity is rare with all classes of antiretrovirals (156,157).

Which therapy first

In cases in which CD4 T lymphocyte count is below 200 cells/µL, HAART represents the most beneficial initial intervention in those with HIV-HCV co-infection (III). In cases in which the CD4 T lymphocyte count has never fallen below 350 x 10^9 cells/L, the strategy of first treating HCV and then HIV in order to avoid the combined toxicities of co-administration of these medications may be considered (C)(III). In those with CD4 T cell count between 200 and 350 x 10^9cells/L, there may be cases in which HAART can be deferred in favour of initial HCV therapy. This is reasonable in the absence of opportunistic infection and markers of rapidly progressive HIV disease (i.e., high HIV viral load). Initiation of both therapies simultaneously is not recommended, given the potential for combined toxicity (D)(III).

Adjuvant therapy

Although there may be situations in which adjunctive therapies including pre-HCV drug therapy antidepressants and erythropoietin may be of value in improving quality of life (158), additional scientific data to support the efficacy of these interventions in HIV-HCV co-infection is required. Management of injection drug use, alcohol use, and depression should be optimized prior to initiating HCV drug therapy as these negatively impact therapeutic success (C)(II).

Transplantation

Liver transplant for the HIV-HCV co-infected subjects with liver failure is being evaluated in a research setting. Further research into the efficacy and safety of this therapeutic option is required. Patients with liver failure should be assessed individually and referred for transplantation, if appropriate.

Vaccination

HAV and HBV vaccination are recommended (C)(II).

Conclusions

The management of chronic viral hepatitis is complex, whether it be hepatitis B or hepatitis C. There are insufficient hepatologists, gastroenterologists and infectious disease specialists in Canada to allow all patients to receive specialist care. It is therefore incumbent on non-specialists caring for these populations to familiarize themselves with the contents of this document, to recognize the limitations of their knowledge, and to refer patients for specialist attention when required. Only in this manner will the population with chronic viral hepatitis in Canada receive the care they deserve.

Addendum

The recommendations for screening in pregnancy contained in this document differ from the recommendations of the National Advisory Committee on Immunization and the Health Canada Canadian Immunization Guidelines - 2002.

Health Canada recommends adherence to the following guidelines:

All pregnant women should be routinely tested for HBsAg at the first prenatal visit and repeat testing before delivery may be considered in uninfected and unimmunized women with continuing high-risk behaviour.

For guidance in assessing high-risk behaviours for Hepatitis B infection see the 1998 Canadian STD Guidelines available on the Health Canada website: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/std-mts98/index.html

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Table 1. Grading system for ranking recommendations and clinical guidelines (3)

Strength of Recommendation		Definition
	A	Good evidence to support a recommendation for use/action
	B	Moderate evidence to support a recommendation for use/action
	C	Poor evidence to support a recommendation for use/action
	D	Moderate evidence to support a recommendation against use/action
	E	Good evidence to support a recommendation against use/action
Quality of Evidence	I	Evidence from one or more properly randomized controlled trial
	II	Evidence from one or more well-designed clinical trials, without randomization, or from cohort or case-controlled analytic series (preferably from >1 centre), or from multiple time series, or from dramatic results from uncontrolled experiments
	III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports from expert committees.

Table 2. Contraindications to antiviral treatment

Alpha Interferon	Ribavirin	Both interferon and ribavirin
Severe or uncontrolled psychiatric disease	Pregnancy or inadequate contraception (males and females)	Documented poor compliance
Hepatic decompensation	Severe heart disease	Ongoing and untreated alcohol or drug abuse
Solid organ transplantation (except liver)	Advanced renal failure	Any other uncontrolled serious medical illness
Certain autoimmune diseases, especially autoimmune hepatitis	Hemoglobinopathy	
Poorly controlled epilepsy	Severe anemia	
Neutrophils <0.75 x 109/l		
Platelet count <40 x 109/l		
Active serious infection		

Notes