

The management of chronic viral hepatitis: A Canadian consensus conference 2004

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Several government and nongovernment organizations held a consensus conference on the management of acute and chronic viral hepatitis to update previous management recommendations. The conference became necessary because of the introduction of new forms of therapy for both hepatitis B and hepatitis C. The conference issued recommendations on the investigation and management of chronic hepatitis B, including the use of lamivudine, adefovir and interferon. The treatment of hepatitis B in several special situations was also discussed. There were also recommendations on the investigation and treatment of chronic hepatitis C and hepatitis C-HIV coinfection. In addition, the document makes some recommendations about the provision of services by provincial governments to facilitate the delivery of care to patients with hepatitis virus infection. The present document is meant to be used by practitioners and other health care providers, including public health staff and others not directly involved in patient care.

Key Words: *Adefovir; Chronic viral hepatitis; Interferon; Lamivudine*

La prise en charge de l'hépatite virale chronique : La conférence consensuelle cana- dienne de 2004

Plusieurs organismes gouvernementaux et non gouvernementaux ont tenu une conférence consensuelle sur la prise en charge de l'hépatite virale aiguë et chronique pour mettre à jour les recommandations de prise en charge antérieures. La conférence s'imposait en raison de l'adoption de nouvelles formes de traitement de l'hépatite B et de l'hépatite C. La conférence a permis de diffuser des recommandations sur l'investigation et la prise en charge de l'hépatite B chronique, y compris le recours à la lamivudine, à l'adéfovire et à l'interféron. Le traitement de l'hépatite B dans plusieurs situations spéciales a également été abordé. Des recommandations ont aussi été émises sur l'investigation et le traitement de l'hépatite C chronique et de la co-infection par l'hépatite C et le VIH. De plus, le document contient des recommandations sur la prestation de services par les gouvernements provinciaux, afin de faciliter la prestation des soins aux patients atteints d'une infection au virus hépatique. Ce document est conçu pour être utilisé par les praticiens et les autres dispensateurs de soins, y compris le personnel de la santé publique et d'autres intervenants ne participant pas directement aux soins des patients.

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 (HBV). The HCV-infected population is heterogeneous and includes those infected through the blood supply, contaminated injection drug use equipment and the 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 coinfecting with HIV and other infections. In contrast, HBV in Canada 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 and incarcerated populations, and in 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 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

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element of what needs to be a comprehensive approach. To maximize the chances of successful therapy and minimize 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 HCV, is 'labour intensive'. This limits the number of patients an individual physician can take care of. The provision of specialized nursing care would 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 a 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, guide best prevention and comprehensive care practices and 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 health care needs across the continuum of prevention, care and treatment.

INTRODUCTION

The management of infection from 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-alpha 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* (3), as well as on various Web sites. The current conference was jointly planned by the Canadian Association for Study of the Liver, the Canadian Infectious Disease Society, 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 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, HCV 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) (4). These levels of evidence are given in italics 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 HBV and HCV 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 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 and territorial reimbursement plans to define categories of patients who were eligible for reimbursement for 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, and a relatively small proportion is 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. 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 (*Level 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 the management of hepatitis, just as there are nurses trained to manage diabetes and cancer, and to provide palliative care. Financial support for the development of hepatitis clinics is also strongly recommended.

The present 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.

HBV

Prevention of HBV infection

Universal vaccination against HBV is effective in preventing the transmission of disease (*Level I*) (5,6). In Canada, where chronic HBV infection is largely a disease of immigrants (7), some provinces offer neonatal vaccination, while others offer preadolescent vaccination. Because chronic HBV is the largest reservoir for the transmission of disease, neonatal vaccination may be preferable in provinces with a high proportion of immigrants from areas of the world highly endemic for HBV. In these populations, horizontal transmission in childhood is more likely (*Level II*) (8,9).

In neonates, the use of the HBV vaccine and HBV immune globulin is highly effective in preventing HBV transmission (*Level I*) (10,11). Furthermore, once infected, the risk of a neonate developing chronic infection is greater than 90% (*Level II*) (12,13). Therefore, screening of pregnant women in the third trimester of pregnancy for hepatitis B surface antigen (HBsAg) is mandatory (*Level A; I*). There are also Canadian economic data indicating that this is a highly cost-effective strategy (14).

TREATMENT OF CHRONIC HBV

Assessment

Baseline assessment should include HBV serology (HBsAg/anti-HBs, hepatitis B e antigen [HBeAg]/anti-HBe), and tests of disease activity (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) and 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) (*Level A; II*). Liver histology, although not mandatory, is highly recommended in patients with active disease (*Level A; II*). Patients with mild disease may not require treatment despite active viral replication.

All HBV carriers should be offered testing for anti-HIV antibodies (*Level A; I*). Although the prevalence of HIV is low in some populations (eg, 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

TABLE 1
Grading system for ranking recommendations and clinical guidelines

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	Definition
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.

Data from reference 4

antibodies should also be measured because HBV-HCV coinfection may impact on the selection of treatment (*Level A; I*) (15).

Hepatitis A (HAV) vaccination is recommended in patients with chronic HBV (*Level B; II*) (16,17).

HBV and hepatocellular carcinoma

Because of the increased risk of developing hepatocellular carcinoma (HCC), it is recommended that patients with chronic HBV undergo regular surveillance to detect early HCC (*Level C; III*) (18,19). However, the risk is not equal in all infected individuals. Patients with established cirrhosis are at highest risk, but patients with noncirrhotic 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 white) are at much lower risk (*Level A; II*) (20,21). 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 alpha-fetoprotein every six months is common practice. However, what little evidence exists suggests that annual surveillance is just as effective (22,23).

Who should be treated?

Acute HBV infection does not require antiviral therapy (*Level B; III*).

HBV-infected individuals, whether HBeAg-positive or HBe-negative with elevated AST and/or ALT, and HBV-DNA levels greater than 100,000 copies/mL are candidates for therapy (*Level A; I*). When the HBV-DNA is less than 100,000 copies/mL, the likelihood of HBV-induced injury is thought to be low (24). The distinction between

HBeAg-positive and HBeAg-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 should response to treatment be assessed?

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 (*Level I*) (25). 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) (26). An alternate endpoint for a partial virological response is a decrease in serum HBV-DNA to less than 100,000 copies/mL (27). A biochemical response is defined as a normalization of serum AST and ALT. Liver biopsy is not mandatory to assess treatment efficacy (*Level B; II*) (27). Response is initially assessed while on therapy (on-treatment response). For patients treated with time-limited regimens (eg, 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 and interferon are both acceptable as initial treatment (*Level A; I*).

Interferon in HBeAg-positive patients: Treatment should consist of 10 million international units (MIU) interferon- α subcutaneously three times per week (TIW) or 5 MIU subcutaneously daily for 16 weeks (*Level I*) (27-32). Some believe that longer duration therapy (up to 24 weeks) may be justified in selected cases (33), such as those with high viral loads (greater than 10^8 copies/mL). A partial virological response (HBeAg seroconversion) may be expected in 25% to 40% of patients six months after the completion of therapy. Response rates are decreased in the presence of high viral loads (greater than 10^8 copies/mL), mild hepatic inflammation (AST or ALT less than $1.5 \times$ the upper limit of normal [ULN]), age over 40 years, presence of cirrhosis and male sex.

The durability of HBeAg seroconversion after interferon treatment in white populations is high (68% three years after stopping therapy) (*Level II*) (34). However, in other populations (eg, South East Asian), the durability of seroconversion may be lower (*Level III*) (35,36).

In white populations, interferon therapy has been shown to enhance overall survival and complication-free survival in HBeAg-positive patients who maintain post-treatment seroconversion (*Level II*) (37). The effect of interferon therapy on survival in Asian populations may not be as pronounced (36,38).

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 may 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 MIU TIW subcutaneously to 10 MIU TIW subcutaneously 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 (*Level II*) (39-41).

Lamivudine in HBeAg-positive patients: The recommended dosage is 100 mg subcutaneously daily for up to five years or more, until a partial virological response (HBeAg seroconversion) occurs, or until lamivudine resistance develops (*Level I*) (42-44). A partial virological response (HBeAg seroconversion) can be expected in 18% to 25% of patients within the first year of therapy, rising to approximately 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 (*Level II*) (45).

There are several areas of uncertainty concerning lamivudine resistance. Phenotypic resistance is defined as the reappearance of HBV-DNA following initial disappearance using a nonpolymerase chain reaction (non-PCR)-based assay, or by a rise in HBV-DNA concentration to greater than 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 (46) and, therefore, the utility of confirming phenotypic resistance by genotyping is unclear. Once resistance occurs (approximately 60% after four years of therapy) (47), it is unclear whether lamivudine should be withdrawn. Disease severity does appear to progress once resistance develops (47,48), 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 (47). 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 once resistance develops. Once lamivudine 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 by mouth daily) (*Level I*) (49-51). The optimal duration of treatment is uncertain. For patients with a biochemical and virological response (eg, normal AST, ALT, and HBV-DNA less than 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 approximately 13% of patients remain in remission. Possible end points for stopping treatment might be negative HBV-DNA by PCR or negative hepatitis B core antigen 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 HBV, 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 (*Level I*) (52,53) that will soon be available in Canada. Although initially studied as first-line therapy for chronic HBV, 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 (54). Because 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 (55), but experience is limited. The durability of seroconversion in HBeAg-positive patients remains unknown. As with all forms of HBV 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 (peginterferon) 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 peginterferon is at least comparable with that of standard interferon (56).

Special indications

HBV in children: The principal goals of therapy of HBV in children are to reduce horizontal and vertical transmission of infection and 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% to 16% of children per year will undergo HBeAg seroconversion (57,58). In Asian children with normal ALT, the rate may be 2% to 5% per year and 11% per year in those with elevated ALT (59,60). Thus, by 20 years of age, as many as 80% of children will undergo spontaneous HBeAg seroconversion in regions of low or moderate endemicity and 25% to 70% in regions of high endemicity (58,60,61). Predictors of spontaneous seroconversion include ALT greater than $3 \times$ ULN, high histological activity index, female sex and low HBV-DNA (ie, 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 control patients have the same rates of seroconversion (60,61), suggesting that treatment mainly accelerates seroconversion by approximately 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 less than 5%); and do not always present in adolescents 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-alpha 6 MIU/m² subcutaneously (maximum 10 MIU) TIW for 24 weeks has been approved for children

with HBeAg-positive HBV. This will achieve a partial virological response in approximately 35% of children (*Level I*) (62). 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% (*Level I*) (63). Therefore, treatment may be appropriate in HBeAg-positive adolescents who have failed to undergo spontaneous HBeAg seroconversion despite ALT greater than $2 \times$ ULN for six to 12 months. In younger patients, moderate or severe inflammation on liver biopsy may also justify treatment (*Level 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 (*Level III*). Children should also be entered into long-term monitoring programs, to detect complications such as HCC (*Level III*).

Pregnant women: Some recommend the use of lamivudine in pregnant women with high HBV-DNA levels to reduce the risk of neonatal transmission (*Level III*) (64). To date, there are no reports of fetal injuries due to lamivudine. A single study (64) has shown that if the HBV-DNA levels are very high (greater than 10^9 copies/mL), the rate of maternal-fetal transmission is approximately 30% despite neonatal vaccination.

Decompensated cirrhosis: Interferon is contraindicated in these patients. Lamivudine is the first choice in patients with active viral replication (HBV-DNA greater than 100,000 copies/mL) (*Level I*) (65,66). 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 (less than 100,000 copies/mL) is doubtful, and lamivudine should not be used under these circumstances (*Level B; III*).

HBV-HCV coinfection: Some favour the use of interferon, because it may be effective in both infections (*Level III*). The most appropriate method of combining interferon and ribavirin has not been established. However, no firm recommendations can be made regarding the use of interferon versus lamivudine.

Renal transplant candidates: Lamivudine treatment is recommended in all HBsAg-positive patients before and following kidney transplantation to avoid HBV reactivation following immunosuppression after transplantation (*Level II*) (67). Whether lamivudine should be used in patients with markers of past HBV infection (anti-HBs-positive and/or anti-hepatitis B core antigen-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: All patients undergoing chemotherapy or bone marrow transplant (BMT) should be screened for HBV markers before treatment (*Level B; II*). In those who are positive for HBsAg, pre-emptive lamivudine treatment should be used to prevent flares of HBV that can occur with these treatments (*Level II*) (68). Because 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 (eg, after BMT), lamivudine therapy should also continue. However, once all courses of chemotherapy have been completed, lamivudine can be withdrawn (*Level C*). Some suggest a period of maintenance therapy of a few months after chemotherapy before withdrawal (*Level 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 HBV infection (*Level II*) (69). 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 (*Level II*). **HIV and HBV infection:** Lamivudine should never be used as monotherapy for HBV infection in untreated HIV patients because the rapid development of HIV resistance to lamivudine may jeopardize future treatment in these cases (*Level 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 coinfecting patients (*Level II*).

The prevalence of HBV-HIV coinfection is approximately 5% but variable depending on location (70). HBV is more active and liver fibrosis is often more advanced in HBV-HIV coinfection compared with HBV infection alone (71,72). Anti-HBs and HBsAg screening should be performed in all HIV seropositive individuals (*Level A; II*). Vaccination is recommended for those negative for HBsAg and anti-HBs. Because the HIV population in general is hyporesponsive to HBV vaccination, either a schedule using a double dose (73), or six standard doses (74), is advised (*Level A; II*). HAV virus vaccination is also recommended (*Level B; II*) (75,76). A multidisciplinary approach for the delivery of care is ideal for the management of HIV-HBV coinfection, including specialists in infectious diseases and hepatology or gastroenterology (*Level C; III*).

In the case of HIV-HBV coinfection, highly active anti-retroviral therapy (HAART) regimens containing the nucleoside reverse transcriptase inhibitors (NRTI) lamivudine and/or tenofovir are ideal given that these drugs possess virological activity against both HIV and HBV and infrequently cause hepatotoxicity (*Level B; II*) (77).

Adefovir should not be used because the dose used to treat HBV (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 coinfecting patient. The rates of aminotransferase normalization, reduction in HBV-DNA to undetectable levels, loss of HBeAg and development of anti-HBe are comparable among interferon, lamivudine and tenofovir (78-80). An advantage of tenofovir over lamivudine may be the slower evolution of drug resistance and the efficacy of tenofovir in individuals with lamivudine-resistant HBV (80,81).

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

There are additional treatment issues around HBV that were not addressed in this conference. These include the

management of hepatitis D, the prevention and treatment of HBV infection in liver transplantation recipients and the treatment of HBV in hemodialysis patients.

HCV

Initial assessment

Initial evaluation of suspected HCV infection involves serological testing for antibodies against HCV (third generation enzyme-linked immunoassay). Testing for HCV should be undertaken in all patients with abnormal aminotransferase levels and in those with risk factors for HCV infection (*Level A; II*). Risk factors include prior injection drug use, even if remote and only occasional, transfusion of blood products before 1990, and being an immigrant from countries with high prevalence rates of HCV. In many countries from which Canada draws immigrants, large numbers of patients were infected with HCV 30 to 50 years ago, related to medical procedures using improperly sterilized syringes and needles (Table 2) (82,83).

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 coinfections such as HBV and HIV. Contraindications to antiviral treatment for HCV are listed in Table 3 (*Level B; II*).

In anti-HCV-positive patients, infection should be confirmed with a highly sensitive qualitative HCV-RNA assay (*Level A; II*). It is impossible to treat HCV properly without viral load and genotype testing. Therefore, viral load and genotype testing has to be available in a timely fashion (*Level 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 before treatment should include genotype, HCV-RNA levels where appropriate (see later), complete blood count, prothrombin time, international normalized ratio, albumin, AST, ALT, bilirubin, alkaline phosphatase, HBsAg, HIV, thyroid stimulating hormone, antinuclear antibodies, glucose, creatinine, serum or urine beta-human chorionic gonadotropin (to exclude pregnancy) and urinalysis (*Level B; II*). Additional tests include abdominal ultrasound and electrocardiogram (if over 50 years of age or history of cardiac disease) (*Level B; II*). Liver biopsy remains the most sensitive measure of disease severity and is recommended but is not mandatory before the initiation of therapy (*Level B; II*). Patients with genotype 2 and 3 infection, who have a high likelihood of cure, may not need a liver biopsy before treatment (*Level B; I*).

Sexually active females must have a pregnancy test before initiation of therapy because of the teratogenicity of ribavirin (*Level B*). Because urinary pregnancy testing has limited sensitivity and can result in false negative readings, serological 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 peginterferon and

TABLE 2
Estimated numbers of immigrants to Canada with chronic hepatitis C (1960 to 2001)

Country of birth	Number infected	Country of birth	Number infected
China	9985	Pakistan	1904
Vietnam	9053	Germany	1741
Philippines	8376	Italy	1577
Egypt	6476	Fiji	1340
India	5664	Sri Lanka	1310
South Korea	4232	United Kingdom	1212
Taiwan	4026	Guyana	1253
United States	3331	Hong Kong	1178
Trinidad	3192	Tanzania	1159
Romania	2707	Greece	1137
Poland	2526	Russia	1083
		Iran	1080
		Haiti	1053
		Lebanon	1008
Total			77,601

Data from R Remis, personal communication

ribavirin, all patients, no matter what the apparent state of their liver disease, should undergo evaluation to determine whether therapy is appropriate (*Level 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 or less six months after the completion of therapy (84,85). 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 (86). For practical purposes, a SVR is equivalent to a cure, with fewer than 2% suffering a late relapse (*Level I*) (86).

Drug treatment

The best results have been obtained using a combination of peginterferon and ribavirin (*Level A; I*) (87,88). Viral genotype has the most profound influence on the likelihood of treatment response. Manns et al (87) have reported an SVR of 42% in genotype 1 patients using peginterferon-alpha-2b at a dose of 1.5 µg/kg subcutaneously weekly, together with ribavirin 800 mg daily for 48 weeks. This was superior to combination

TABLE 3
Contraindications to antiviral treatment for hepatitis C

Alpha interferon	Ribavirin	Both interferon and ribavirin
Severe or uncontrolled psychiatric disease	Pregnancy or inadequate contraception (males and females)	Documented poor compliance
Hepatic decompensation		Ongoing and untreated alcohol or drug abuse
Solid organ transplantation (except liver)	Severe heart disease	Any other uncontrolled serious medical illness
Certain autoimmune diseases, especially autoimmune hepatitis	Advanced renal failure	
Poorly controlled epilepsy	Hemoglobinopathy	
Neutrophils <0.75x10 ⁹ /L	Severe anemia	
Platelet count <40x10 ⁹ /L		
Active serious infection		

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 mg to 1200 mg by mouth is a more suitable dose for genotype 1, depending on whether the patient is less than or heavier than 75 kg (*Level I*) (89). Fried et al (88) have reported a similar SVR of 44% in genotype 1 patients using peginterferon-alpha-2a at a dose of 180 µg subcutaneously per week plus ribavirin, 1000 mg to 1200 mg by mouth daily. The initial registration studies for peginterferon/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 (*Level B; II*).

Genotype 2 and 3 infection is optimally treated with a 24-week regime using peginterferon-alpha-2a, 180 µg subcutaneously weekly or peginterferon alpha-2b, 1.5 µg/kg subcutaneously (*Level I*). A fixed dose of 800 mg ribavirin by mouth daily is sufficient when using either peginterferon-alpha-2a or -2b (*Level A*) (85,87). SVRs of 78% to 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 (eg, less than approximately 800,000 IU/mL) (87-89).

There are currently two preparations of peginterferon. 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 United States and in Europe, the two drugs, peginterferon and ribavirin, are available separately. While there are advantages to bundling, the major drawback is a loss of flexibility to increase 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)

(87, 88,90). 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

For patients infected with genotype 1, the likelihood that an individual patient will have an SVR can be reliably predicted after 12 weeks of therapy by assessing the early virological response (EVR) (*Level 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% to 3% chance of achieving an SVR. Therapy should therefore be stopped for these patients (*Level A; I*) (88,91). Those achieving an EVR have a 65% to 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 with baseline at 12 weeks of therapy (*Level B; III*). Patients who achieve a 1.8 log drop 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 (*Level C; III*). Those who fail to clear the virus at 24 weeks should have therapy withdrawn, because they are extremely unlikely to achieve SVR (*Level A; I*) (89,91). 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 (92).

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 (*Level 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 nonresponder to interferon and relapsed during or after treatment.

Evaluation and monitoring during treatment

Treatment of HCV 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 complete blood count at weeks 1, 2, 4, 6 and 8, and then monthly. ALT, bilirubin, glucose and urinalysis should be done monthly, thyroid stimulating hormone and weight every three months (*Level B; I*) (93,94). 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 (95,96). The manufacturers also suggest that if the neutrophil count falls below $0.8 \times 10^9/L$, the dose of interferon should be reduced. However, studies (97) suggest that even at neutrophil counts of $0.5 \times 10^9/L$, infection is rare. 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 (88,98).

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 (99). Studies show that the use of erythropoietin allows the ribavirin dose to be maintained. However, there are no data as yet on the effect that this might have on SVR rates. Granulocyte-macrophage colony stimulating factor and granulocyte colony stimulating factor (G-CSF) have been used to treat interferon-induced neutropenia. The use of erythropoietin and granulocyte-macrophage colony stimulating factor or G-CSF are controversial, and add significant expenses, but may be appropriate in some patients (100-102).

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) (103-105). Although the majority of these patients have mild disease on biopsy, a few may have significant fibrosis (106-110). Treatment with peginterferon and ribavirin results in equivalent SVR rates in patients with normal ALT, compared with patients with abnormal ALT (111). Therefore, patients with persistently normal ALT should be considered for therapy (*Level 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 may 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) (97). These patients should no longer be automatically refused treatment (*Level C; II*). Unacceptable declines in cell counts during therapy may respond to growth factor therapy (see above).

Acute HCV: Acute HCV is rarely identified because the majority of patients are asymptomatic during the initial stage of infection. Because some patients may present before the development of anti-HCV antibodies, the diagnosis requires the demonstration of HCV-RNA in serum (112). Approximately 40% to 50% of symptomatic patients (eg, those with jaundice, nausea, vomiting, right upper quadrant discomfort or influenza-like symptoms) will clear the virus spontaneously (113,114). 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 (*Level B; II*) (115). In asymptomatic patients, immediate treatment can be considered due to the low probability of spontaneous viral clearance (114) and high rates of successful treatment when administered during the early period of infection (*Level II*) (115). Although data from randomized controlled trials are lacking, the highest rate of SVR (98%) has been reported with high dose induction therapy with standard interferon monotherapy (five million units (MU) subcutaneously daily for four weeks followed by 5 MU subcutaneously TIW for 20 weeks) (*Level B; II*) (115). 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 HCV have mild disease, a significant proportion will progress to cirrhosis. The majority of the complications of chronic HCV, including liver failure, variceal bleeding and HCC, occur exclusively in these patients (116). Therefore, cirrhotic patients have the most to gain from successful antiviral therapy. Unfortunately, rates of SVR 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 (*Level B; II*) (117). In patients with compensated cirrhosis, the optimal therapy is the combination of peginterferon and ribavirin (*Level B; II*). Subgroup analyses of the large registration trials of this therapy revealed rates of SVR of 43% to 44% (in patients with bridging fibrosis and cirrhosis combined) (87,88). The dosage and duration of therapy should be the same as in noncirrhotic patients; however, dosage reductions may be necessary in patients with pre-existing cytopenias. Adjunctive therapy with growth factors including erythropoietin 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 (*Level D; III*).

Extrahepatic manifestations of HCV: There are several conditions related to HCV that may 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.

Retreatment of patients: Selected patients who have failed to respond to interferon-based therapy should be considered for retreatment. The decision to retreat patients should consider the previous therapy received, the tolerance of and response to prior treatment (nonresponse versus relapse), and factors predictive of an SVR. Patients with advanced fibrosis (stage 2 or greater) should be given priority for retreatment (*Level C; II*). 'Relapsers' become HCV-RNA-negative during treatment (as manifested by an EVR or end-of-treatment virological response), but have reappearance of HCV-RNA following the withdrawal of therapy. 'Nonresponders' fail to achieve HCV-RNA negativity during treatment. The latter group is more resistant to retreatment 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 retreatment strategy (*Level B; II*). In relapsers and nonresponders to interferon and ribavirin combination therapy, retreatment with peginterferon-alpha and ribavirin can be considered, although efficacy data from randomized controlled trials are not currently available (*Level III*). Preliminary data suggest that approximately 10% of nonresponders and approximately 20% of relapsers achieve an SVR (118,119). 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 (95). 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 (96). Ribavirin is contraindicated in patients with significant renal dysfunction (creatinine clearance below 50 mL/min) due to altered pharmacokinetics and the risk of severe anemia. Ribavirin has been used, however, in specialized care centres at low dosages with therapeutic monitoring of plasma ribavirin concentration (120). In patients with previous renal transplantation, interferon is contraindicated due to the risk of precipitating irreversible graft dysfunction (*Level II*) (121).

Children with chronic HCV: Although the progression of chronic HCV appears slower in children than in adults (122), some children have significant fibrosis on liver biopsy (*Level 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 HCV are typically asymptomatic and the majority have normal or minimally elevated serum aminotransferases (*Level II*) (123). Because the correlation between ALT and hepatic histological lesions is poor, a liver biopsy should be considered in the management of infected children, particularly after 10 years of infection (*Level C; III*). Patients with moderate to severe fibrosis and/or necroinflammatory activity on liver biopsy should be targeted for therapy, preferably at specialized centres (*Level C; III*). Standard interferon (3 MU/m² TIW) and ribavirin (15 mg/kg/day) for 48 weeks yields rates of SVR similar to that observed in adults (40% to 60% overall, 70% to 100% in genotypes 2 and 3) (*Level II*) (124,125). The efficacy of peginterferon and ribavirin has yet to be conclusively demonstrated. Interferon is generally well-tolerated in children; weight loss, the only side effect, presents more frequently in children than in adults. The resultant growth inhibition is not permanent (126). Children younger than three years of age should not be treated due to concerns regarding the potential neurotoxicity of interferon on the developing brain (127) and the higher rates of spontaneous viral clearance observed in this subgroup.

HIV-HCV COINFECTION

Approximately one-quarter of Canadian HIV-infected individuals are seropositive for HCV (128). Among HIV seropositive injection drug users, this rate is at least 50% and up to 80% in some regions (129). Since the introduction of HAART, liver disease secondary to HCV infection has become a leading cause of morbidity and mortality in HIV-HCV coinfection (130). Progression to cirrhosis and decompensated liver disease is accelerated in HIV-HCV coinfecting patients (131-133). Immunodeficiency (CD4 less than 200 cells/µl) and excess alcohol consumption (greater than 50 g/day) are independently associated with rapid progression to cirrhosis. The influence of HCV on HIV infection is less pronounced (134,135). CD4 T cell recovery following initiation of HAART may be blunted in comparison with HCV seronegative individuals with HIV

(136,137). Mildly elevated aminotransferases, biopsy inflammation scores and liver fibrosis may be improved in HIV-HCV coinfecting subjects receiving potent and durable HAART, compared with baseline (138,139).

Screening and investigations

HCV screening by serology is recommended in all HIV-infected individuals (*Level 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 (eg, patients with abnormal liver enzymes in the absence of other causes of liver disease or patients at high risk for acquiring HCV infection). Liver biopsies in HIV-HCV coinfection identify at least some disease activity in most patients (greater than 95%) (140). In one study, three-quarters of HIV-HCV coinfecting 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 cirrhotic patients who may be at more risk of treatment-related hepatotoxicity (*Level A; II*).

Treatment environment

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

HCV drug therapy

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

The SVR rate with 48 weeks of peginterferon-alpha-2 plus ribavirin for genotype 1 infection is under 30% (*Level I*) (140-144). 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 the end of therapy and the 72 week follow-up (*Level I*) (141-143). It is unclear if 24 weeks of therapy is sufficient, because a 29% relapse rate has been reported after the end of therapy for genotype 3 infections (140). The EVR, defined as at least a 2 log drop in HCV viral load, should be determined because the lack of an EVR predicts failure to achieve SVR (*Level 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 because SVR rates are reduced with subtherapeutic dosing in HCV monoinfected patients (*Level B; II*).

The constitutional and cognitive toxicities related to therapy are significant (144), but in general, are not more frequent or severe in comparison with those infected with HIV alone. Therapy in this population is often contraindicated because of comorbid 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) (*Level I*) (145-147).

Because both zidovudine and ribavirin can cause anemia, careful attention is warranted if coadministered (*Level C; II*) (148). Although ribavirin may alter the intracellular levels of several NRTIs (149), neither increased treatment side effects nor loss of HIV virological suppression have been reported in NRTI-treated subjects initiating ribavirin.

Use of antiretrovirals

There is a risk of hepatotoxicity with antiretroviral therapy (150,151). Hepatic steatosis and fulminant hepatitis are rare complications of HIV NRTI treatment (151-155). These toxicities are mediated by NRTI inhibition of mitochondrial DNA replication (152). Severe elevation of aminotransferases (defined as greater than $10 \times$ ULN) occurs in 5% to 10% of patients; most protease inhibitors (153-155) are usually asymptomatic and resolve without interruption of antiretroviral therapy. However, the patient should be monitored closely for signs of liver failure. A 2% to 4% incidence of rise in aminotransferases is reported in treatment-naïve subjects receiving non-NRTIs (152). An early nevirapine hypersensitivity syndrome consisting of fever, rash and elevated ALT has also been described but is infrequently observed (155,156). Treatment-limiting hepatotoxicity is rare with all classes of antiretrovirals (157,158).

Which therapy first

In cases in which CD4 T lymphocyte count is below 200 cells/ μ L, HAART represents the most beneficial initial intervention in those with HIV-HCV coinfection (*Level III*). In cases in which the CD4 T lymphocyte count has never fallen below 350×10^9 cells/L, the strategy of first treating HCV and then HIV to avoid the combined toxicities of coadministration of these medications may be considered (*Level C; III*). In those with CD4 T cell count between 200×10^9 cells/L and 350×10^9 cells/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 (eg, high HIV viral load). Initiation of both therapies simultaneously is not recommended, given the potential for combined toxicity (*Level 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 (159), additional scientific data to support the efficacy of these interventions in HIV-HCV coinfection are required. Management of injection drug use, alcohol use and depression should be optimized before initiating HCV drug therapy because these negatively impact therapeutic success (*Level C; II*).

Transplantation

Liver transplantation for HIV-HCV coinfecting 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 (*Level C; II*).

CONCLUSIONS

The management of chronic viral hepatitis is complex, whether it be HBV or HCV. There are insufficient hepatologists, gastroenterologists and infectious disease specialists in Canada to allow all patients to receive specialist care. It is therefore incumbent on nonspecialists 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.

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