Executive Summary

A meeting of a panel of experts in the fields of hepatology, infectious disease, virology, addictions, primary care, education and guideline development, as well as appropriate patient representatives was convened. Participants were asked to review and critically evaluate currently available literature relevant to the management of hepatitis C (HCV) and human co-immunodeficiency viral (HIV) infection. Data were presented to the group, discussed and formulated into guidelines. Funding for the meeting and the development of these guidelines were provided by the Hepatitis C Division of Health Canada.

The population of individuals co-infected with HCV and HIV living in Canada is estimated to be > 5000. The majority will have acquired their infections using illegal intravenous drugs or by exposure to contaminated blood products. Populations with increased rates of co-infection are those who are residing in prisons, aboriginals, women with HIV, street people, and persons with hemophilia and other congenital coagulation disorders.

It is timely to develop management guidelines for the HCV/HIV co-infected individual as therapy with highly active antiretroviral therapy (HAART) has markedly improved the prognosis of HIV infected persons. Individuals with HIV who are co-infected with HCV can develop significant HCV related liver disease, causing an increase in both morbidity and mortality in this

population. Antiviral therapy for HCV can now eliminate detectable virus (HCV RNA) in serum in 40% of HIV negative patients treated with a combination of IFN? 2b and ribavirin (30% and 65% for genotypes 1 and 2-3 respectively). A sustained virological response is associated with improvement in liver histology, which may be reasonably assumed to lead to an improved long-term survival from liver disease,

Recent management guidelines for the treatment of HIV and for HCV are available. Therapy of HCV/HIV co-infection poses additional management issues, which need to be specifically addressed in order to maximize therapeutic efficacy. Substance dependence is prevalent in the IVDU population and this behavior impairs adherence to treatment regimens and places individuals at risk for re-infection. Regular alcohol consumption even in moderate amounts is associated with more rapid progression of liver fibrosis. It is imperative that these issues be addressed before initiating therapy for either viral infection. Access to therapy may be an additional problem for those who are homeless or who live in isolated, rural areas or who are incarcerated.

Controversy exists as to which viral infection should be treated first. Before that decision is made, it is important that the co-infection be identified. Therefore, screening for co-infection is important when patients present with either infection.

There is data that suggests anti-retroviral therapy for HIV may be associated with greater hepatoxicity in HCV infected individuals. Conversely " immune reconstitution" of the HIV infected subject upon the introduction of HAART may enhance HCV immune mediated liver disease if co-infection is present. In general, given the current responses to antiretroviral therapy, it is recommended that HIV infection be addressed (and treated where appropriate), first, with introduction of HCV therapy at a later date in the appropriate patient. At the present time assessment of the severity of liver disease present can only be established by examination of liver histology, and treatment is only recommended for those who on liver biopsy has at least moderate inflammation and/or fibrosis. If successful clearance of HCV infection can be achieved in the HCV/HIV co-infected subject it is hoped that both the morbidity and mortality from both infections will be reduced.

Antiretroviral therapy can be initiated with either protease inhibitor containing or protease inhibitor sparing regimens. The choice of the specific agents in the combination must take into consideration issues of adherence and toxicity in the coinfected patient. If specific therapy for HCV is being considered, agents with overlapping toxicity should be avoided.

Peer reviewed data on the outcome of antiviral therapy for HCV in individuals also infected with HIV are sparse and mostly limited to interferon (IFN) monotherapy. The total number of patients treated is small

and the long-term follow-up data are even less. Those studies published using IFN monotherapy indicate that co-infected individuals respond, although maybe not as well, as persons only infected with HCV, in terms of loss of detectable serum HCV RNA at the end of treatment and at 6 months of follow-up. Therapy with IFN?2b and ribavirin (the current standard of care for HCV in those without contraindications and who meet the criteria for treatment) is also reported to be effective in those with HCV/HIV co-infection, but the numbers treated are so small that they are not generalizable. However it seems reasonable to use IFN?2b plus ribavirin in the co-infected patient as in the HIV negative patients. The duration of antiviral therapy for HCV is determined by baseline genotype. The optimal duration of therapy in the co-infected patient is unclear.

There are several concerns regarding factors that may limit efficacy and the safety of treatment of HCV and HIV when simultaneous infections are present. They are:

1. Due to issues of toxicity and adherence, under most circumstances, it is unwise to initiate both therapeutic regimens simultaneously.
2. Adherence to dual therapy for HCV and HIV may be compromised by prior or ongoing problems with substance dependence, synergistic side effects, accessibility to therapy and overwhelming “drug fatigue”.

3. There are potential drug interactions, which could reduce the efficacy or toxicities of HAART.
4. Bone marrow toxicity of HAART may preclude using an adequate dose of antiviral therapy (ribavirin) for HCV.

In order to try to avoid untoward drug interactions and toxicities, certain modifications to the recommended management/therapeutic regimens for both HCV and HIV may be required. These include:

a) Increased frequency of monitoring of plasma HIV RNA is recommended when a subject is taking both HAART and IFN?2b because of the theoretic potential for competitive inhibition of thymidine kinases required for drug phosphorylation (ribavirin and nucleoside reverse transcriptase inhibitors).
b) The ability of the bone marrow to respond to ribavirin induced hemolysis in the face of multiple bone marrow suppressive drug therapies should be monitored by the reticulocyte response.
c) In patients with HIV being treated with certain protease inhibitors, e.g.: indinavir which may cause unconjugated hyperbilirubinenemia due to displacement from albumin needed for liver cell uptake, the hemoglobin may be the more reliable measure of hemolysis due to ribavirin, than increases in bilirubin.

d) Recidivism in former IVDU may be precipitated by IFN therapy, thus promoting failure to adhere to all prescribed treatments and thus promoting the development of viral resistance to both HIV and HCV. In addition, this behavior may place the patient at risk of re-infection, thus ongoing addiction counseling may be needed.

e) "Immune reconstitution" following the introduction of HAART for HIV may "activate" chronic hepatitis C and potentially may initiate hepatic

f) Decompensation in a patient with cirrhosis. Liver function tests need to be monitored during therapy – albumin, bilirubin, INR.

g) HAART may exhibit greater hepatoxicity in individuals infected with HCV – thus there is a need to establish that any abnormality of liver enzymes in co-infected individuals is due to HCV and not due to a hepatoxic drug reaction prior to initiating therapy for HCV. Further, liver biochemistry must be monitored carefully during therapy.

The guidelines provide detailed recommendations for the diagnosis and treatment of the co-infected patient, and aim to heighten awareness of practicing physicians as to who should be screened, investigated and treated for HCV and HIV co-infection.