Position Paper

Strategic Initiatives: Addressing the Epidemic of HIV and Hepatitis Co-Infection in British Columbia

Prepared for the Honorable Colin Hansen
Minister of Health Services

March, 2003

Prepared by Paula Braitstein, MA, MSc, Phd (Cand)
Senior Policy Advisor on Health Promotion
British Columbia Persons with AIDS Society

Introduction

Although the BC Persons with AIDS Society has long been aware of the magnitude of the HIV-Hepatitis C co-infection epidemic in British Columbia, it is only recently that the treatment and care obstacles facing people who are co-infected have come directly to our attention. The experience of one of our members in particular has magnified several systemic issues of critical significance to the appropriate care and management of persons who are co-infected. The purpose of the present document is to highlight these issues, and make recommendations regarding how best to address them. The issues can be broadly broken down into three categories:

1) Routine patient management issues
2) Pharmacare issues
3) Solid organ transplantation

It should be noted that a multi-stakeholder meeting regarding the care, treatment, and support of co-infected individuals and the prevention of new HIV / HCV infections that took place on January 24, 2003, independently raised and agreed upon virtually all the recommendations which follow (see Appendix One for the Final Report from this meeting).

Background

What is Hepatitis C?

Hepatitis C is a virus that directly affects the liver by infecting liver cells. Ultimately this process leads to the destruction of the liver [1]. In people who are mono-infected with Hepatitis C (i.e. those who only have Hepatitis C and not HIV), 10-20% will progress to end-stage liver disease in approximately 25 – 30 years. In people who are HIV-HCV co-infected, twice that number, 20-30%, will progress to end-stage liver disease at 2 – 3 times the rate, or in 7 to 10 years. Although there is presently no vaccine for Hepatitis C, the disease is potentially curable through the use of combination antiviral therapy. This is in contrast to HIV, for which although there are treatments available to suppress viral replication, it is impossible to cure because the virus integrates into an infected individual's genome. HCV does not enter the genome and is considered a curable illness.

How is Hepatitis C Spread?

Hepatitis C is spread by blood, as is HIV. The two most documented routes of transmission are the use of blood products, and unsafe injection drug use. However, Hepatitis C is a highly infectious agent, hundreds of times more infectious than HIV, and is also spread through unprotected sexual contact, the use of intranasal cocaine equipment, non-sterile acupuncture needles and tattooing equipment [2].

Who is Co-Infected?

It is estimated that as much as 3% of the world's population is infected with the Hepatitis C virus (HCV) [3], including an estimated 1% of Canadians [4]. In British Columbia, there have been 43,000 reported cases Hepatitis C, but the BC Center for Disease Control believes this is a significant underestimate of the actual number of people chronically infected with the virus [5].

As of December, 2002, the United Nations had estimated that there were 42 million people living with HIV/AIDS in the world [6], including approximately 40,000 in Canada [7], of whom between 10,000-15,000 live in British Columbia.

HIV and Hepatitis C share many routes of transmission. In Canada and elsewhere in the Developed World, it is estimated that as many as 30% of individuals who have HIV also have Hepatitis C [8-10]. Thus although the number of co-infected individuals is relatively small compared to the number of people who are mono-infected (4000 vs. 40,000), this group of individuals requires more specialized and more intensive treatment and care than either HIV or HCV mono-infected patients.

Why is Co-Infection with HIV and Hepatitis C Problematic?

There is an important negative synergy between the two viruses. People who are co-infected with HIV and Hepatitis C have faster rates of liver fibrosis and development of cirrhosis compared to HCV mono-infected individuals [11-19], poorer responses to Hepatitis C treatment [10, 20-25], and overall worse survival [10, 14, 26-30]. Importantly, HCV is harder to detect in people who are HIV-positive using standard antibody techniques, presumably because of an impaired immune response [31].

However, these negative outcomes are partially alterable through a variety of factors. These include the patient's CD4 count and other immunological factors when they begin treatment [32-35], the type and length of Hepatitis C treatment they receive [20-22, 36-40], and whether they are using antiretroviral therapy for HIV infection at the same time [24, 34, 41-48].

The use of Highly Active Antiretroviral Therapy (HAART) has largely transformed HIV disease into a chronic, manageable illness [43]. However, most antiretroviral agents are metabolized through the liver, and can cause varying degrees of liver toxicity [46, 47]. Despite the gains made by the use of antiretroviral therapy, viral co-infection with Hepatitis C is becoming a leading cause of morbidity and mortality among people living with HIV [16, 49-51], and viral co-infection can further exacerbate drug-related hepato-toxicities [49, 52, 53].

The Situation in British Columbia Today

In broad terms, the situation for co-infected individuals in British Columbia today is not very hopeful. Although co-infected individuals are filling the HIV Ward at St. Paul's hospital, there is little to offer them. The burden of this combined epidemic is only beginning to be understood. Research from the BC Center for Excellence in HIV/AIDS shows that although two years ago Hepatitis C was not an independent predictor of death among HIV-positive individuals receiving antiretrovirals, today it is [54]. Part of the reason for this is that the majority of co-infected individuals became infected with HIV and/or Hepatitis C during the outbreak among injection drug users in the mid- to late- 1990's. Given an average progression rate of their liver disease of 7 to 10 years, one can see that the medical complications are only beginning to surface. British Columbia is currently poorly equipped to deal with this emerging problem.

There are, however, several areas in which there are key opportunities to make significant improvements in the way in which people who are HIV/HCV co-infected are medically managed.

Routine Patient Management Issues

Problem: Hepatitis C in the presence of HIV is a much more aggressive and complicated disease than in people who only have Hepatitis C, and seriously complicates the ability to manage HIV disease.

People who are co-infected need to be tested early in their HCV disease, and tested with more elaborate methods (i.e. PCR-based techniques which detect the actual virus instead of just antibodies to the virus). People who are co-infected need to be treated earlier in the course of their HCV disease, and they often require longer treatment than people who are mono-infected. People who are co-infected need to coordinate their HIV and Hepatitis C treatments, since factors

which predict treatment success in people who are co-infected include receiving treatment at a high CD4 count, before beginning HIV treatment with antiretrovirals. There are several other treatment and care related issues that are unique to people who are co-infected, indicating the need for a coordinated, evidence-based approach to the management of Hepatitis C among HIV-infected individuals.

***Solution**: Empower the BC Center for Excellence in HIV/AIDS to medically manage co-infected individuals.*

Based on the model of managing HIV in the province, empowering the BC Center for Excellence in HIV/AIDS to manage Hepatitis C in people with HIV would enable:

- *the development of evidence-based, state-of-the-art therapeutic guidelines for co-infection*
- *the management of accidental exposures to Hepatitis C (they already manage accidental exposures for HIV)*
- *the appropriate training of health care providers*
- *the cost-effective distribution of Hepatitis C drugs to eligible co-infected individuals*

Pharmacare Issues

Problem 1: The best available, federally licensed treatment for Hepatitis C (pegylated interferon) is not covered by Pharmacare. Physicians are postponing treating their patients until the pegylated interferon is covered because it is approximately twice as effective with many fewer toxicities.

***Solution**: Immediately provide Pharmacare coverage for pegylated interferon for the treatment of Hepatitis C infection.*

Problem 2: Currently available treatment, Rebetron (a combination of regular interferon with ribavirin) is only available to individuals for 6 months, but research shows that the majority of people requiring treatment require at least 48 weeks of therapy. This results in prolonged treatment interruptions which severely compromises the opportunity to treat the disease effectively.

***Solution**: Change Pharmacare policy to automatically allow patients to continue their Hepatitis C treatment for as long as it is required or recommended by their physicians.*

Problem 3: Currently available treatment, Rebetron, has substantial bone-marrow toxicities, for which medication is available but not approved by

Pharmacare. Patients frequently have to discontinue their Hepatitis C treatment due to these toxicities.

***Solution**: Provide Pharmacare coverage of erythropoeitin and G-CSF to manage the side effects associated with Hepatitis C treatment.*

Solid Organ Transplantation

Problem 1: Hepatitis C is the leading cause of liver transplantation in the Developed World. Until recently, however, HIV has been considered an absolute contraindication to solid organ transplantation. Although the BC Transplant Society (BCTS) has developed a policy for HIV and transplantation, there are several outstanding issues which pose significant barriers to the timely and appropriate assessment and listing of HIV-positive individuals. These include:

- the need to assess people living with HIV more quickly than individuals without HIV because their liver disease progresses more quickly, and because their liver disease significantly impairs the ability to manage HIV;
- the requirement that people with HIV be taking antiretrovirals as a condition of getting activated on the waiting list is ethically problematic when the act of taking antiretrovirals poses immediate life threatening consequences to the individual because of their advanced liver disease and the substantial liver toxicities associated with antiretroviral medications.

***Solution**: Adoption by BCTS of adopt evidence-based and appropriate criteria, consistent with current knowledge regarding the management of HIV disease.*

Problem 2: There is a shortage of viable organs in this province for transplantation. Furthermore, the BCTS has no experience with transplantation in HIV-infected individuals.

***Solution** Given that there is considerable experience with organ transplantation in HIV-infected individuals in the United States, the BC government, through BCTS, should financially support three to five HIV-positive individuals to receive transplants in the United States, as provided for under the "Medical Services Commission Out of Province and Out of Country Medical Care Guidelines for Funding Approval". This endeavour would enable the BCTS to acquire expertise in this area, as well as saving several lives.*

An Ounce of Prevention

Clearly one of the most important approaches to addressing HIV/HCV co-infection is to prevent new infections, and to prevent those who are already

infected from developing end-stage liver disease. Preventing new infections can be accomplished through the immediate implementation of harm reduction strategies (such as more needle exchange programs, and safe injection facilities), and addiction treatment (note that the 17 beds designated for detoxification for women in British Columbia is shamefully inadequate).

Preventing people from progressing in their disease or slowing that progression down can be accomplished through providing access to the best available HCV medications on the market (i.e. pegylated interferon), providing access to medications to manage the toxicities associated with these medications, and providing access to medications for as long as they are medically required (note that most people do not require more than 48 weeks of therapy, in contrast to HIV treatment which is lifelong). The second major opportunity for preventing or slowing disease progression among co-infected individuals is to empower the BC Center for Excellence in HIV/AIDS to coordinate and manage Hepatitis C treatment and care for HIV-infected individuals.

Summary and Conclusions

Although British Columbia is currently facing the beginning of a dual epidemic with a high case-fatality rate, there are opportunities available to mitigate the damage.

We urge the BC government to show leadership in addressing this important issue by implementing the recommendations provided within this paper, and substantiated through the multi-stakeholder consensus meeting report on co-infection held in January, 2003.

References

1. Davis, G., *Hepatitis C,* in *Schiff's Diseases of the Liver*, E.R. Schiff, Editor. 1999, Lippincott-Raven: Philadelphia.
2. Alter, M., *et al., The prevalence of hepatitis C virus infection in the United States, 1988 through 1994.* New England Journal of Medicine, 1999. **341**: p. 556-62.
3. Lavanchy, D., *Global surveillance and control of hepatitis C.* Journal of Viral Hepatitis, 1999. **6**: p. 35-47.
4. Canada, H., *Epidemiology of the transmission of blood-borne pathogens,* . 1997, Laboratory Centre for Disease Control.
5. Control, B.C.f.D., *Annual Summary of Reportable Diseases,* . 2001, BC Center for Disease Control: Vancouver.
6. AIDS, U., *AIDS epidemic update,* . 2002, Joint United Nations Programme on HIV/AIDS: Geneva.

7. Canada, H., *HIV/AIDS Epi Update,* . 2000, Laboratory Centre for Disease Control.
8. Sherman, K.E., *et al., Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group.* Clinical Infectious Diseases, 2002. **34**(6): p. 831-7.
9. Patrick, D.M., *et al., Incidence of hepatitis C virus infection among injection drug users during an outbreak of HIV infection.* Cmaj, 2001. **165**(7): p. 889-95.
10. Bonacini, M. and M. Puoti, *Hepatitis C in patients with human immunodeficiency virus infection: diagnosis, natural history, meta-analysis of sexual and vertical transmission, and therapeutic issues.* Arch Intern Med, 2000. **160**(22): p. 3365-73.
11. Benhamou, Y., *et al., Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group.* Hepatology., 1999. **30**(4): p. 1054-8.
12. Benhamou, Y., *et al., Factors affecting liver fibrosis in human immunodeficiency virus and hepatitis c virus coinfected patients: impact of protease inhibitor therapy.* Hepatology, 2001. **34**: p. 283-287.
13. Bonacini, M., *et al., Patients co-infected with HIV and hepatitis C virus demonstrate higher levels of hepatic HCV RNA.* Journal of Viral Hepatitis, 1999. **6**(3): p. 203-8.
14. Di Martino, V., *et al., The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study.* Hepatology, 2001. **34**(6): p. 1193-9.
15. Garcia-Samaniego, J., *et al., Influence of hepatitis C virus genotypes and HIV infection on histological severity of chronic hepatitis C.* American Journal of Gastroenterology, 1997. **92**(7): p. 1130-4.
16. Graham, C.S., *et al., Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis.* Clin Infect Dis, 2001. **33**(4): p. 562-9.
17. Puoti, M., *et al., Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus.* Journal of Infectious Diseases, 2000. **183**(1).
18. Rai, R., *et al., Severity and correlates of liver disease in hepatitis C virus-infected injection drug users.* Hepatology, 2002. **35**(5): p. 1247-55.
19. Talal, A.H., P.W. Canchis, and I. Jacobson, *The HCV and HIV Coinfected Patient: What Have We Learned About Pathophysiology?* Curr Gastroenterol Rep, 2002. **4**(1): p. 15-22.
20. Cotler, S.J. and D.M. Jensen, *Treatment of hepatitis C virus and HIV co-infections.* Clin Liver Dis, 2001. **5**(4): p. 1045-61.
21. Gaglio, P.J., *et al., The effect of HIV coinfection on hepatitis C: A review.* J La State Med Soc, 2001. **153**(11): p. 552-8.

22. Fukuda, M., *et al., Predictive factors in eradicating hepatitis C virus using a relatively small dose of interferon.* Journal of Gastroenterology & Hepatology, 1998. **13**(4): p. 412-8.
23. Liang, T., *et al., Pathogenesis, Natural History, Treatment, and Prevention of Hepatitis C.* Annals of Internal Medicine, 2000. **132**(4): p. 296-305.
24. Pol, S., A. Vallet-Pichard, and H. Fontaine, *Hepatitis C and human immune deficiency coinfection at the era of highly active antiretroviral therapy.* J Viral Hepat, 2002. **9**(1): p. 1-8.
25. Tedaldi, E. and P. Bean, *Diagnosis, evaluation, and treatment of HIV/HCV coinfection.* Am Clin Lab, 2001. **20**(9): p. 26-32.
26. Garcia-Samaniego, J., *et al., Hepatocellular carcinoma in HIV-infected patients with chronic hepatitis C.* Am J Gastroenterol, 2001. **96**(1): p. 179-83.
27. Greub, G., *et al., Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: The Swiss HIV Cohort Study.* Lancet, 2000. **356**: p. 1800-1805.
28. Silvestri, F., *et al., Impact of hepatitis C virus infection on clinical features, quality of life and survival of patients with lymphoplasmacytoid lymphoma/immunocytoma.* Annals of Oncology, 1998. **9**(5): p. 499-504.
29. Staples, C.J., D. Rimland, and D. Dudas, *Hepatitis C in the HIV Atlanta Veterans' Affairs Cohort Study.* Clinical Infectious Diseases, 2000. **29**(1): p. 409-10.
30. Yee, T.T., *et al., The natural history of HCV in a cohort of haemophilic patients infected between 1961 and 1985.* Gut, 2000. **47**(6): p. 845-51.
31. Braitstein, P., *et al. Dangerous Oversights: A comparison of HCV-RNA testing vs. HCV-antibody testing among HIV-infected individuals.* in *Canadian Association for HIV Research.* 2001. Toronto, Canada.
32. Chung, R., *et al., Immune recovery is associated with persistant rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects.* AIDS, 2002. **16**(14): p. 1915-1923.
33. Daar, E.S., *et al., Relation between HIV-1 and hepatitis C viral load in patients with hemophilia.* J Acquir Immune Defic Syndr, 2001. **26**(5): p. 466-72.
34. Greub, G., *et al., Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study.* Lancet, 2000. **356**(9244): p. 1800-5.
35. Yokozaki, S., *et al., Immunologic dynamics in hemophiliac patients infected with hepatitis C virus and human immunodeficiency virus: influence of antiretroviral therapy.* Blood, 2000. **96**(13): p. 4293-9.
36. Cozzolongo, R., R. Cuppone, and O.G. Manghisi, *The Treatment of Chronic Hepatitis C not Responding to Interferon.* Curr Pharm Des, 2002. **8**(11): p. 967-75.
37. Ikeda, K., *et al., Long-term interferon therapy for 1 year or longer reduces the hepatocellular carcinogenesis rate in patients with liver cirrhosis caused by*

hepatitis C virus: a pilot study. Journal of Gastroenterology & Hepatology, 2001. **16**(4): p. 406-15.

38. Rodriguez-Rosado, R., *et al.*, *Management of hepatitis C in HIV-infected persons.* Antiviral Res, 2001. **52**(2): p. 189-98.
39. Schlaak, J.F., *et al.*, *Sustained suppression of HCV replication and inflammatory activity after interleukin-2 therapy in patients with HIV/hepatitis C virus coinfection.* J Acquir Immune Defic Syndr, 2002. **29**(2): p. 145-8.
40. Thibault, V., *et al.*, *Interleukin 2 treatment does not modify hepatitis B or C replication in human immunodeficiency virus-infected patients: results from a randomized control trial.* Hepatology, 2002. **35**(1): p. 238-9.
41. Bruno, R., P. Sacchi, and G. Filice, *Mitochondrial toxicity in HIV-HCV coinfection: It depends on the choice of antiretroviral drugs?* Hepatology, 2002. **35**(2): p. 500-1.
42. Filippini, P., *et al.*, *Can HCV affect the efficacy of anti-HIV treatment?* Arch Virol, 2000. **145**(5): p. 937-44.
43. Hogg, R., *et al.*, *Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens.* CMAJ: Canadian Medical Association Journal, 1999. **160**(5): p. 659-65.
44. Lafeuillade, A., G. Hittinger, and S. Chadapaud, *Increased mitochondrial toxicity with ribavirin in HIV/HCV coinfection.* Lancet, 2001. **357**(9252): p. 280-1.
45. Nunez, M., *et al.*, *Risk factors for severe hepatic injury after introduction of highly active antiretroviral therapy.* J Acquir Immune Defic Syndr, 2001. **27**(5): p. 426-31.
46. Sulkowski, M., *et al.*, *Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection.* JAMA, 2000. **283**(1): p. 74-80.
47. Sulkowski, M.S., *et al.*, *Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections.* Hepatology, 2002. **35**(1): p. 182-9.
48. Yeni, P.G., *et al.*, *Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel.* Jama, 2002. **288**(2): p. 222-35.
49. Bica, I., *et al.*, *Increasing Mortality Due to End-Stage Liver Disease in Patients with Human Immunodeficiency Virus Infection.* Clinical Infectious Diseases (CID), 2001. **32**(Feb 1): p. 492-497.
50. Neff, G., D. Jayaweera, and A. Tzakis, *Liver transplantation for HIV-infected patients with end-stage liver disease.* Current Opinion in Liver Transplantation, 2002. **7**(2): p. 114-123.
51. Soriano, V., *et al.*, *Impact of chronic liver disease due to hepatitis viruses as cause of hospital admission and death in HIV-infected drug users.* European Journal of Epidemiology, 1999. **15**: p. 1-4.

52. Gonzalez de Requena, D., *et al., Liver toxicity caused by nevirapine.* Aids, 2002. **16**(2): p. 290-1.
53. Reisler, R., *et al. Risk of Grade IV Events and Death in HIV Patients Co-Infected with Hepatitis B and/or Hepatitis C Receiving HAART*. in *9th Conference on Retroviruses and Opportunistic Infections*. 2002. Seattle, WA.
54. Braitstein, P., *et al. Hepatitis C is an independent predictor of mortality among a population-based treatment cohort of antiretroviral naive individuals initiating triple-combination therapy*. in *Canadian Association for HIV Research*. 2003. Halifax.

Roadmap for Addressing the Epidemic
of HIV and Hepatitis C Co-Infection in Canada:

Issues, Recommendations, Priorities and Next Steps

June, 2004

Report from the National Stakeholders Meeting on Improving Access to Care, Treatment, and Support for People Living with HIV and Hepatitis C Co-infection, Montreal, Quebec, January 2004.

Dedication

This report is dedicated in loving memory to Glen Edward Hillson, for whom knowledge about and action on these issues did not happen fast enough.

Preamble

The Canadian Treatment Action Council (CTAC) is a national, non-profit, consumer-driven organization dedicated to improving the lives of people living with HIV/AIDS by promoting informed public policy and public education, and promoting awareness of issues that impact access to treatment and health care for people living with HIV/AIDS.

Over the course of 2003, CTAC, with the financial support of Schering-Plough Canada and Agouron/Pfizer, sponsored a series of regional fora in Vancouver, Montreal, Toronto, and Halifax, regarding treatment and care issues in HIV and Hepatitis C co-infection. In January, 2004, these fora culminated in a multidisciplinary gathering of 50 people living with HIV and/or HCV co-infection, physicians (including general practitioners, hepatologists, and gastroenterologists), epidemiologists, and people working in community organizations, correctional settings, government, and the pharmaceutical industry (see Appendix One). The national meeting was supported by Schering-Plough, Hoffmann-LaRoche, the Anemia Institute, Agouron/Pfizer, ShireBioChem/GlaxoSmithKline, Bristol Myers Squibb, Abbott Laboratories, and Boehringer Ingleheim.

The purpose of CTAC's regional fora and national meeting was to identify barriers to the appropriate treatment, care and support of people who are co-infected, and to identify mechanisms and the key players involved in moving past those barriers. The national meeting was intended to produce a report that would serve as a 'roadmap' of where we are in Canada with the epidemic of HIV/hepatitis C co-infection in terms of treatment and care issues, where we need to go, and how we can get there.

This document is a summary and synthesis of that national meeting, bolstered by other relevant information and recommendations where appropriate, and was prepared by Paula Braitstein (Board Member, Canadian Treatment Action Council (CTAC), Senior Policy Advisor on Health Promotion, BC Persons with AIDS Society (BCPWA)).

CTAC would like to thank the organizers of the meeting, including Louise Binder, James Kreppner, Philip Lundrigan, Paula Braitstein, Sheena Sargent, Patrick McIntyre, Claire Checkland, Kim Thomas, Lorne Fox, Marie Prevost, Susan Redgrave, Daryle Roberts, Daryn Bond, Françoise Grothé, and Marlene Allan. CTAC would like to gratefully acknowledge the work of the notetakers, Chantale Perron and Terry Pigeon. Last but not least, the organizing committee would like acknowledge and thank Mardie Serenity for her logistical wizardry, excellent minutes, attention to detail, and generally keeping it all together!

Table of Contents

List of Acronyms

AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase (a liver enzyme)
APRICOT	AIDS Pegasys Ribavirin International Co-Infection Trial
ASO	AIDS Service Organization
BCPWA	British Columbia Persons with AIDS Society
CAHR	Canadian Association for HIV Research
CanFAR	Canadian Foundation for AIDS Research
CASL	Canadian Association for the Study of the Liver
CIHR	Canadian Institutes of Health Research
CSHA	Canadian Strategy on HIV/AIDS
CTAC	Canadian Treatment Action Council
CTN	Canadian HIV Trials Network
EPO	erythropoietin
FRSQ	Fédération de Recherche de la Société Québécoise
HAART	Highly Active Antiretroviral Therapy
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
LCDC	Laboratory Centre for Disease Control
MAT/DOT	Maximally Assisted Therapy/Daily Observed Therapy
MSFHR	Michael Smith Foundation for Health Research
OHTN	Ontario HIV Treatment Network
PASAN	Prisoners' HIV/AIDS Support Action Network
VANDU	Vancouver Area Network of Drug Users

Executive Summary

Hepatitis C and HIV co-infection is an important Canadian health issue that is not receiving the attention it demands. Hepatitis C affects approximately 30% of people living with HIV (and approximately 10% of those infected with hepatitis C are also infected with HIV). Co-infected individuals are more likely to be Aboriginal, young, current or former injection drug users, current or former inmates, and people who received contaminated blood or blood products in the course of their healthcare. The majority of people who are co-infected live in Montreal or Vancouver, with emerging epidemics in Ottawa, Toronto, Calgary, and Edmonton.

In the presence of HIV, hepatitis C disease progression takes place 2 to 3 times faster, compared to people who only have hepatitis C. Thus, in seven to fifteen years after becoming infected, approximately 50-70% of co-infected people will begin to develop liver inflammation, and at least 20-30% will progress to liver fibrosis and cirrhosis, including end-stage liver disease. Because of the rapidity of disease progression in co-infected individuals, and their often unique constellation of social and health needs (e.g. in dealing with addiction, mental health, and HIV treatment issues), co-infected people represent a distinct population, falling between the cracks of both HIV and Hepatitis C treatment systems. HIV care providers and community services are ill-equipped, under-funded, and often lack sufficient or appropriate information on hepatitis C. Hepatitis C care providers are sometimes uninterested in HIV issues or HIV-positive people and often also require education and awareness training on HIV. Hepatitis C community services are almost non-existent, in part because of the lack of leadership by the Federal government (approximately 1% of Canadians are believed to be infected with hepatitis C, yet Canada has no national Hepatitis C Strategy or dedicated funding).

The average onset of HIV symptoms in the absence of treatment is seven to ten years after infection. The onset of fibrosis or scarring of the liver due to hepatitis C in the presence of HIV is seven to fifteen years. Many individuals who are currently co-infected acquired their two viruses together, and many of them became dually infected in the 1990's. Because of this, there is urgency to address the unique issues arising from the convergence of these epidemics.

The purpose of CTAC's regional fora and national meeting was therefore to identify barriers to the appropriate treatment, care and support of people who are co-infected, and to identify mechanisms and the key players involved in moving past these barriers. The meeting was intended to produce a report that would serve as a 'roadmap' of where we are in Canada with the epidemic of HIV/hepatitis C co-infection in terms of treatment and care issues, where we need to go, and how we can get there.

Areas identified as needing particular attention were:

- Clinical issues including access to treatment, management of side effects, balancing HIV management, psychiatric and mental health supports, transplantation, and health care delivery

- Defining research priorities
- Policy issues ranging from federal and provincial strategies and funding, to formulary drug coverage and transplantation
- Prevention education, including primary and secondary prevention
- Community support services
- Correctional settings

Advocacy Priorities

Short-term:

- Identify best practices and standards of care for HIV/HCV co-infection.
- Advocate with provincial and private payers to broaden criteria for accessing treatment, and to cover concomitant Growth Factors, if necessary.
- Update treatment and management guidelines for co-infection, including HCV treatment issues, HIV treatment issues, side effect management, transplantation, nutritional issues, and psychiatric issues (expand upon what is contained in the CASL 2004 viral hepatitis guidelines).
- Disseminate treatment and management guidelines widely.
- Work with CTN to expand their HCV co-infection 'Core' as a basis for a network of investigators in co-infection.
- Have provincial transplant centers and the Canadian Society of Transplantation develop appropriate guidelines for the assessment and transplantation of HIV co-infected individuals.
- Identify pharmacoeconomists who can conduct research into the cost-effectiveness of properly addressing HIV/HCV co-infection, and the cost-effectiveness of treatment, and those who are willing to work with community activists to decipher existing materials.
- Use advocacy issues, such as lack of access to treatment, to raise public awareness and apply pressure on government through media campaigns.

Long-term:

- Develop a national observational cohort of co-infected individuals, on and off treatment.
- Expand CTAC's Post-Approval Surveillance System project to incorporate HCV treatments.

Next Steps

1. CTAC to disseminate meeting report to all meeting participants, and other relevant stakeholders who did not attend.
2. CTAC to organize a national meeting of key clinicians, scientists, and consumers, to develop a research agenda for distribution to all research funding bodies (including the pharmaceutical industry, CIHR, OHTN, and CTN).
3. National state-of-the-art co-infection treatment and management guidelines should be developed and published.

4. CTAC's Co-Infection sub-committee to identify individuals interested in working together to develop workplan priorities to continue this work, including following-up on priorities highlighted in this report.
5. Advocate with the federal government for the immediate establishment of an on-going National Hepatitis C Strategy, appropriately resourced (as per the Canadian AIDS Society document entitled "A National Hepatitis C Strategy in Canada: A Discussion Paper", www.cdnaids.ca).
6. PASAN to circulate updated information regarding co-infection in correctional settings.
7. HepCure BC to conduct a survey on the availability of HCV treatment across the country, and disseminate findings (see Appendix Two).

Summary of Recommendations by Stakeholder

Federal Government

- Fund and implement an ongoing national hepatitis C strategy that significantly incorporates HIV co-infection.
- Incorporate priorities regarding co-infected individuals into the CSHA, with extra dollars attached.
- Devote more money to researching clinical aspects of co-infection, including natural history and pathogenesis issues.
- Create a network of databases for sharing data regarding treatment outcomes among co-infected individuals, and a network of physicians and researchers focussing on co-infection.
- Establish Centers for Excellence in Hepatitis C with expertise in HIV co-infection.
- Provide sufficient financial resources to allow integrated and specialized clinics to operate.
- Immediately implement and fund more harm reduction and addiction treatment services.
- Fund AIDS Service Organizations and other community-based organizations to provide resources and materials to co-infected individuals.
- Pressure the Canadian Society for Transplantation to develop appropriate guidelines for transplantation in HIV-infected individuals.
- The Ministerial Council on HIV/AIDS should advise the federal HIV/AIDS Division to incorporate HCV co-infection into the revised CSHA, with the recommendation of attaching not currently allocated dollars.
- Include significant participation from both HIV and hepatitis C groups in the membership of all federal government committees addressing either HIV or hepatitis C issues.
- Classify hepatitis C as an AIDS defining illness, and classify addiction as a disability (where it is not already).
- Support, fund, and implement general and targeted education campaigns aimed at increasing the number of people getting tested for both viruses, and at decreasing the stigma associated with having them. Health Canada should lead and fund these initiatives, in collaboration with grassroots organizations and the provincial government.

Provincial Governments

- Expand eligibility criteria for accessing and remaining on hepatitis C treatment for as long as patient and physician believe it necessary and appropriate.
- Recognize and accept that the cost of growth factors is part of the cost of HCV treatment; then negotiate with the companies that make hepatitis C treatments, and those that make the growth factors, to enable the combined usage at a reduced cost.
- Develop provincial Hepatitis C Strategies, with devoted money, paying particular attention to addressing clinical management and community support issues.

- Identify what specialized services, in terms of HCV treatment and HIV co-infection, are available in Canada, and where they are available.
- Regularly revise treatment and management guidelines based on current evidence, and disseminate widely to physicians and patients.
- Ensure that each province has appropriate guidelines for liver transplantation in HIV-infected individuals.
- Develop Centers for Excellence in Hepatitis C with expertise in HIV co-infection.
- Provide sufficient financial resources to allow integrated and specialized clinics for coinfection to operate.
- Immediately fund and implement more harm reduction and addiction treatment services.
- Support, fund, and implement general and targeted education campaigns aimed at increasing the number of people getting tested for both viruses, and at decreasing the stigma associated with having them. Health Canada should lead and fund these initiatives, in collaboration with grassroots organizations and the provincial government.
- Include significant participation from both HIV and hepatitis C groups in the membership of all provincial government committees addressing either HIV or hepatitis C issues.

- Classify addiction as a disability (where it is not already).
- Fund AIDS Service Organizations and community-based organizations to provide resources and materials to co-infected individuals.

Correctional Services

- Immediately implement recommendations from existing reports regarding safe drug use and tattooing, methadone treatment, addiction treatment, harm reduction, and unhindered access to knowledgeable care providers and specialists.
- Enhance collaboration between existing clinics and hepatitis, HIV, and infectious disease specialists.
- Integrate other health care modalities into all clinics, and move toward a holistic and patient-centered model of care.
- Provide opportunities to see patients in health care settings daily or weekly to assist them with receiving and tolerating their treatments (e.g. daily observed therapy, maximally assisted therapy), and provide adequate nutritional and mental health supports.
- Develop new, or adapt existing, drop-in day clinics to help patients receive and tolerate their treatments.
- Immediately implement more harm reduction and addiction treatment services.
- Launch general and targeted education campaigns aimed at increasing the number of people getting tested for both viruses, and at decreasing the stigma associated with being infected.

Industry

- Make products, including both HCV treatments such as pegylated interferon and also supportive therapies such as erythropoeitin (EPO), more accessible through price reduction and other means.
- Work with public payers to expand eligibility criteria for accessing and remaining on hepatitis C treatment for as long as patient and physician believe it necessary and appropriate.
- Conduct pharmacoeconomic studies to show the cost-effectiveness of supportive treatments such as EPO, and early treatment of HCV infection.
- Participate in the development of a HIV/HCV co-infection research agenda, and integrate these priorities into their drug development plans.
- Devote more money to researching clinical aspects of co-infection, including natural history, pathogenesis issues, HCV treatment, and HIV treatment.
- Always provide an expanded access program for new drugs for hepatitis C, with designated spaces reserved for HIV co-infected individuals.
- Include, and separately analyze, HCV co-infected individuals in research for HIV and HIV-related products.
- Support community initiatives in the areas of harm reduction, addiction treatment, and poverty reduction.
- Support the development of drop-in centers for co-infected persons, including explicit supports for co-infected people on treatment.

Clinicians, Health Care Services, and Health Authorities

- Use clinical authority to advocate that third party payers expand their eligibility criteria for accessing and remaining on hepatitis C treatment for as long as patient and physician believe it necessary and appropriate.
- Encourage public payers and pharmaceutical manufacturers to negotiate the costs of HCV treatment, including growth factors.
- Identify best practices and standards of care elsewhere in the world for the treatment and management of HIV/HCV co-infection.
- Identify what specialized services, in terms of HCV treatment and HIV co-infection, are available in Canada, and where they are available.
- Regularly revise treatment and management guidelines based on current evidence, in consultation with consumers, and disseminate widely to other physicians and patients.
- Refer HIV-positive patients to transplant centers for assessment, even if the transplant center does not have an HIV infection policy, and not wait until the patient has decompensated cirrhosis to refer them.
- Pressure organ transplant centers to develop appropriate policies and guidelines for assessing and performing liver transplants on people living with HIV. Clinicians and surgeons working in transplant centers should be proactive in developing these policies and guidelines.
- Encourage and support existing HIV clinics in working more collaboratively with hepatitis experts.
- Hepatitis experts should become more proactive in learning about HIV and collaborating with HIV experts.

- Move all clinics toward integrating other health care modalities, and toward a holistic and patient-centered model of care.
- Develop Centers for Excellence in Hepatitis C with expertise in HIV co-infection.
- Provide opportunities to see patients in health care settings daily or weekly to assist them with receiving and tolerating their treatments (e.g. daily observed therapy, maximally assisted therapy).
- Develop or adapt drop-in day clinics to help patients receive and tolerate their treatments.
- Implement more harm reduction and addiction treatment services.
- Develop Continuing Medical Education programs specifically to train physicians on co-infection, and develop and offer more training to front-line workers.
- Develop mentorship and training programs in co-infection for physicians and researchers.
- Support efforts to classify hepatitis C as an AIDS defining illness, and addiction as a disability.
- Develop more drop-in centers for persons co-infected with HIV and HCV, including explicit supports for people on treatment.

Scientists

- Conduct pharmaeconomic studies to show the cost-effectiveness of early HCV treatment and the use of supportive therapies such as EPO.
- Regularly revise treatment and management guidelines based on current evidence, in collaboration with consumers, and disseminate widely to physicians and patients.
- Develop an HIV/HCV research agenda in order to identify research priorities across the Four Pillars Drug Strategy (harm reduction, prevention, treatment, enforcement).
- The Canadian Association for HIV Research (CAHR) should write a letter to CIHR, OHTN, CTN, and other research institutions such as CanFAR, to advocate for more money to be devoted to researching various aspects of co-infection, including natural history and pathogenesis issues.
- Develop Centers for Excellence in Hepatitis C with expertise in HIV co-infection.
- The CIHR Advisory Committee on HIV/AIDS and the Federal Ministerial Council on HIV/AIDS should recommend the same thing to these research organizations.
- The Canadian HIV Trials Network should create a network of databases for sharing (anonymized) data regarding treatment outcomes among co-infected, and a network of physicians and researchers focussing on co-infection.
- Research funding bodies such as CIHR, CanFAR, the CTN, and the OHTN should solicit research proposals specific to the issue of HCV/HIV co-infection.

Community Organizations

- Develop and implement more harm reduction services.
- Develop targeted education campaigns aimed at increasing the number of people getting tested for both viruses, and at decreasing the stigma associated with having them.

- Lobby for funding dedicated to HCV/HIV co-infection to be built into the Canadian Strategy on HIV/AIDS, with devoted materials and resources developed as a result.
- Make hepatitis C co-infection a priority in organizational workplans.
- Encourage participation of both HIV-positive and hepatitis C-positive individuals on organizational committees.
- Provide resources and materials to HCV/HIV co-infected individuals about co-infection.
- Develop peer-driven networks and groups to foster mutual support and collective action.
- Develop more drop-in centers for persons co-infected, including explicit supports for people on treatment.

Activists and Consumers

- Have courage, be tenacious, and know your stuff.
- Familiarize yourself with the recommendations for all stakeholders, select the issue(s) that is/are of highest personal importance and/or interest, and actively work towards the achievement of the recommended actions, either as an individual or through an affiliate organization.

Epidemiology and Population Health Issues

According to the World Health Organization, hepatitis C has infected approximately 170 million people globally to date. Africa has the highest prevalence at 5%, suggesting there may be an epidemic of HIV/HCV co-infection lurking there should the HIV epidemic become controlled (. Canada's HCV prevalence is estimated to be 1% (approximately 250,000-300,000 people) many of whom have no idea they are infected. Approximately 10% of people who have HCV also have HIV. In North America and Western Europe, up to 30% of people who are HIV-positive are co-infected with HCV, depending on the primary HIV risk group in a given population (e.g. in parts of Spain, 50-70% of all people with HIV also have hepatitis C because of the prevalent use of injection drugs). In most places, people who acquired HIV through injection drug use or the use of contaminated blood products are very likely to also have hepatitis C. In Canada, Aboriginal people and youth, especially women, people who have ever been incarcerated, and anyone who has used injection drugs, are particularly vulnerable. HCV is much more infectious than HIV, and can be spread through a minute amount of blood. Thus, intranasal cocaine use, or improperly sterilized tattoo or acupuncture equipment, are all risk factors for acquiring HCV.

Worldwide, injection drug use accounts for at least half of all new HCV infections. Like HIV, the populations in which HCV is becoming epidemic are more marginalized. For this reason, addressing the epidemic of HIV/HCV co-infection requires addressing many root causes of poor health and high risk behaviors. These include inadequate, inaccessible, and unaffordable housing, poverty, stigma and discrimination, uncontrolled addictions, and the US-led "War on Drugs", which prevents the government of Canada from widely implementing harm reduction programs or the medical use of marijuana. These issues were raised repeatedly in the meeting, and considered integral and essential to any meaningful solution.

As antiretroviral therapy has extended the length and improved the quality of life of thousands of people living with HIV/AIDS, previously unseen diseases are now emerging in this population. Hepatitis C has become a leading cause of death in people living with HIV/AIDS in countries where people have access to antiretrovirals, including Canada.

Clinical Issues

The Hepatitis C Virus (HCV) is an RNA virus, like HIV, but it differs from HIV in that it does not integrate itself into the host person's DNA. This means that it is possible to eradicate HCV from the body. HCV can cause end-stage liver disease and liver cancer.

The hepatitis C virus is not believed to cause its damage directly. HCV viral load does not correlate well with disease progression, as in the case of HIV, although HCV viral load is an important predictor of treatment success, and a high HCV viral load is believed responsible for the elevated rates of vertical HCV transmission among HIV-co-infected mothers. Rather, it is believed that HCV is an immune-mediated disease, meaning that it

does its damage by disrupting the immune system. Hepatic fibrosis and cirrhosis, or scarring of the liver, is actually the body's healing response to liver damage.

People with HIV are particularly vulnerable to HCV progression. This is likely due, in part, to the poorly understood relationship between hepatitis C and the immune system.

In people who only have HCV, approximately 25-30% will progress to cirrhosis in 20-30 years, while another 50-70% will have on-going liver inflammation without necessarily advancing to end-stage liver disease. The remainder are able to spontaneously clear their virus through an effective immune response. Unfortunately, these natural history data have not been confirmed in HIV-positive people. In people who are immune-compromised, such as those with HIV, HCV accelerates. It is to be expected, given all the other ways that HIV negatively impacts HCV, that a higher proportion of HIV co-infected people will progress to end-stage liver disease. Overall, people who are co-infected with HIV/HCV can expect their HCV infection to progress two to three times faster, so those who are going to progress to end-stage liver disease can expect it to happen, on average, 7-10 years from the time they were infected with HCV.

HIV-positive men, women who are post-menopausal, people who are older than 50, people with lower CD4 counts, and people who drink alcohol are all at greater risk of progressing to end-stage liver disease. The lower the CD4 count, the more vulnerable to liver disease. One study showed that a CD4 count below 500 cells was associated with progression to liver fibrosis, even in people without HIV.

So keeping the immune system strong is important, but the use of antiretroviral therapy can be both beneficial and detrimental to people co-infected with HIV and hepatitis C. The interactions between hepatitis C, immune depletion and restoration, and antiretroviral medications are complex and not well understood. Antiretrovirals are, obviously, instrumental in preventing immune depletion, and in restoring immune function. However they can also be harmful to the co-infected through a variety of mechanisms, all of which need more study:

- hepatitis C related liver disease (i.e. hepatic fibrosis) can become accelerated as a result of immune reconstitution
- hepatitis C viral loads, already elevated in people with HIV, can become further elevated upon starting antiretroviral treatment
- hepatitis C can lead to mitochondrial dysfunction (including fatty liver, lactic acidemia and lactic acidosis, and peripheral neuropathy), insulin resistance, and diabetes – all of which are also potential side effects of antiretroviral medications
- nevirapine and ritonavir are known to be particularly toxic to the liver, and there is insufficient data to know whether low-dose ritonavir is harmful in people who are co-infected
- hepatitis C independently causes severely elevated liver enzymes, and taking antiretrovirals can lead to further elevations and increased clinical symptoms, sometimes resulting in interruptions of the HIV treatment

- antiretrovirals taken together with hepatitis C treatments make treatments even more difficult because of the overwhelming additional toxicity
- people with hepatitis may have poorer immune responses to antiretroviral treatment compared to HIV mono-infected people

Fortunately, moderate advancements are being made in the treatment of hepatitis C. The use of pegylated interferon in combination with ribavirin has improved response rates among both HCV mono-infected and HIV/HCV co-infected. Although no head-to-head study has been conducted to date, data presented at the 11th Conference on Retroviruses and Opportunistic Infections (Feb 2004) suggests that those who are HIV/HCV co-infected will have poorer responses to treatment. The 48-week long APRICOT co-infection study allowed the concomitant use of growth factors to manage ribavirin-associated anemia, used full-dose ribavirin throughout, and used a population of people in their clinical trial who were on average healthier than the target population. Pegylated interferon alpha 2a combined with ribavirin still only achieved a 40% sustained virologic response, including 80% among those with genotype 2/3, but less than 30% among those with genotype 1. The majority of people with hepatitis C in North America and Europe, including those co-infected with HIV, have genotype 1. This was one of three co-infection treatment trials presented at CROI 2004; this was both the most rigorous study in design, and by far achieved the most favorable results.

There are multiple factors that can influence the potential for successful HCV treatment. Many of these factors were identified in the meeting as being barriers to treatment for co-infected people in Canada today. These include:

1. Being able to take the treatment for as long as patient and physician both feel it necessary and appropriate.
    - continued treatment: currently, those with GT1 have their treatment stopped if they haven't achieved at least a 2-log reduction in their HCV RNA by week 12.
    - long-term maintenance treatment: on-going studies (HALT-C) are examining the safety and efficacy of long-term maintenance treatment, and although these data will be years coming, there is evidence now to show that being on treatment, even in the presence of HCV viremia, confers histologic benefit to the liver (i.e. reduces fibrosis and inflammation).
    - treatment in the presence of HIV: HIV co-infection may result in delayed HCV viral clearance after starting HCV treatment, but the virus can be, and is, eventually cleared.
2. Having access to the use of growth factors such as erythropoeitin and GM-CSF/G-CSF.
    - ribavirin-associated anemia: this is one of the most treatment limiting factors, and the use of growth factors has been shown to improve full adherence to ribavirin, as well as improve patients' quality of life (being able to take full dose ribavirin the entire period is predictive of treatment success).
    - cost: treatment with growth factors is expensive, and neither the provincial payers nor the private insurers want to pay, but it is a cost that should simply be considered part of the cost of treating hepatitis C.
3. Being able to start treatment when patient and physician feel it is appropriate.

- decision making: whether and when to treat hepatitis C should be a decision made together by patient and doctor.
- eligibility criteria: numerous eligibility criteria exist across Canada proscribing who can even try treatment, or not. These criteria vary from province to province (see Appendix Two). Examples of requirements include: being completely HCV treatment naïve (including interferon monotherapy), having consistently elevated ALTs, or having evidence of moderate fibrosis (see Appendix Three). These criteria are largely not evidence-based: relapsers from interferon monotherapy, for example, have nearly as high response rates to peglyated interferon plus ribavirin as treatment naïve people do; ALTs are a notoriously bad measure of liver disease (studies have shown that 25% with liver cirrhosis will have normal ALTs); people are known to have more successful treatment outcomes if they don't yet have fibrosis.

4. Having strong psychiatric supports, including consultations with a knowledgeable psychiatrist and access to support groups.
   - Depression: anti-depressants are regularly prescribed preventively when people are starting HCV treatment, because the depression associated with the interferon treatment can be grueling.
5. Having knowledgeable and coordinated care, including HIV specialists, HCV specialists, dieticians, social workers, and nurses.
6. Treat HCV first to make HIV treatment possible.
   - Over 75% of severe cases of HAART-related hepatotoxicity (usually defined as grade 3/4 increases in liver enzymes) occur in those HCV co-infected.
   - Reduce the probability of mitochondrial toxicity or metabolic abnormalities from developing secondary to the hepatitis C.
   - Adherence to HIV treatment is already a challenge.

HCV treatment may only benefit 20-30% of people who are co-infected. Therefore, a broad array of services, supports, and clinical guidelines are required to support those who are chronically infected with HIV and HCV.

Clinical Recommendations and Responsibilities:

- Recommendation: The use of Growth Factors should be considered a standard part of the cost of treating hepatitis C. Public and private payers need to be educated about the importance of growth factors for patients. Pharmaeconomic studies should be performed to show the cost-effectiveness of these supportive treatments. Public payers should negotiate with the companies that make hepatitis C treatments, and those that make the growth factors, to enable their combined usage at a reduced cost.
- Responsibility: Community activist groups and prescribing physicians should target third party payers, both public and private, to encourage them to cover these products. Community activists and physicians should approach leading epidemiologists with pharmacoeconomic specialties to do the appropriate studies.

- Recommendation: Public payers must be pushed into expanding their eligibility criteria for accessing and remaining on hepatitis C treatment for as long as patient and physician believe it necessary and appropriate.
- Responsibility: Third party payers (provincial and private payers), community activists, patients, physicians (both HIV and HCV).

- Recommendation: Identify best practices and standards of care elsewhere in the world regarding the treatment and management of HIV/HCV co-infection.
- Responsibility: Clinicians, scientists, community activists, people co-infected.

- Recommendation: Identify what specialized services, in terms of HCV treatment and HIV co-infection, are available in Canada, and where they are available.
- Responsibility: Provincial representatives to the Canadian Treatment Action Council, community activists, clinicians, health authorities.

- Recommendation: Regularly revise treatment and management guidelines based on current evidence, and disseminate widely to physicians and patients.
- Responsibility: Clinicians, guideline developers, community activists.

Liver Transplantation and HIV

Hepatitis C is the leading cause of liver transplantation in the world. Until 1996, transplants were not an option for people living with HIV/AIDS because the morbidity associated with full-blown AIDS resulted in people not living long enough to benefit from a transplant. Since 1996, however, and the advent of Highly Active Antiretroviral Therapy (HAART), liver transplants have been performed in nearly 100 people living with HIV/AIDS. Overall, the rate of success in terms of patient and graft survival among HIV-positive people is equivalent to that in HIV-negative people. Some factors increase the probability of a successful outcome, including a higher baseline CD4 count, being able to tolerate and respond virologically to antiretrovirals post-transplant, and strong personal and social support. Unfortunately, hepatitis C returns in nearly all cases, and in a significant proportion of people causes cirrhosis of the new liver within 1 – 3 years. However, this also happens in HIV-negative people, and research is underway into how to reduce this adverse outcome.

Based on currently available evidence, recommended criteria for being a transplant candidate are:

- Having a baseline CD4 count of at least 100 cells, preferably 200 cells.
- Being able to respond virologically to HAART post-transplant (i.e. not being multi-drug resistant).
- Meeting other eligibility criteria unrelated to HIV disease, as determined by transplant centers.

Guidelines regarding transplantation are generally a provincial issue, and pressure should be put on provincial transplant centers to develop progressive and evidence-based guidelines regarding HIV and transplantation.

Transplantation Recommendations and Responsibilities:

- Recommendation: Provinces need to develop guidelines for the transplantation of HIV-infected individuals.
- Responsibility: Physicians should refer their HIV-positive patients to transplant centers. Physicians and activists should pressure transplant centers to develop appropriate policies and guidelines for assessing and performing transplants on people living with HIV. Transplant centers should be proactive and responsive to developing these guidelines.

Clinical Research Needs

HIV/HCV co-infection raises a multitude of research questions. These questions pertain to the pathogenesis of HCV and its relationship with the immune system, the interactions between HCV disease and the toxicities of antiretrovirals, and of course issues related to treatment of HCV. Specific research ideas that arose during the meeting were:

- Improved measures of liver disease (to replace biopsies)
- Improved understanding of who to treat, for how long, and how to improve sustained response rates (including reducing or managing side effects)
- The safety and feasibility of maintenance HCV therapy
- Strategies to improve adherence
- The economic burden of HCV disease, and the cost effectiveness of treatment
- Research specific to co-infected IDU's
- The impact of immune suppression, immune restoration, and antiretroviral therapy on the progression of liver disease
- The interactions between HCV disease and the toxicities of antiretrovirals (i.e. insulin resistance, diabetes, mitochondrial damage, etc.): are they additive or multiplicative?
- Primary vaccine research
- New, less toxic, and easier to take treatments
- Developing a National HCV Clinical Trials Network
- Developing a National HCV Research Training program

Research Recommendations and Responsibilities:

- Recommendation: A research agenda should be developed to identify priorities in understanding the natural history of hepatitis C in the presence of HIV, new targets for drug development, and improvements in the currently available treatments.
- Responsibility: Consumers, physicians, independent investigators, pharmaceutical companies. CTAC offered to organize a symposium devoted to developing a co-infection research agenda.

- Recommendation: More money should be devoted to researching clinical aspects of co-infection, including natural history and pathogenesis issues.
- Responsibility: Research funding bodies, including the Canadian Institutes of Health Research (CIHR), the Canadian HIV Trials Network (CTN), the Ontario HIV Treatment Network (OHTN), the Federation de Recherche de la Societe Quebecoise (FRSQ), and the Michael Smith Foundation for Health Research (MSFHR), should all be sensitized to the importance of co-infection, and encouraged to solicit research proposals specific to the issue. The Canadian Association for HIV Research (CAHR) would be well positioned to write a letter to these institutions on this subject, supported by various bodies, such as the CIHR Advisory Committee on HIV/AIDS, and the Federal Ministerial Council on HIV/AIDS. Pharmaceutical companies developing new drugs for hepatitis C should always provide an expanded access program with designated spaces reserved for HIV co-infected individuals. Pharmaceutical companies conducting research in HIV and HIV-related products should always try to do research in the HCV co-infected.

- Recommendation: Create a network of databases for sharing (anonymized) data regarding treatment outcomes among co-infected, and a network of physicians and researchers focussing on co-infection.
- Responsibility: The Canadian HIV Trials Network's Hepatitis C Co-infection Core is best poised and suited for this role.

Health Care Needs

HIV/HCV co-infected individuals by definition represent a distinct patient population. For example, medically they require HIV specialists, HCV specialists, and perhaps addiction specialists, often simultaneously. Treating the HIV without considering the HCV, or treating the HCV without considering the HIV, could be disastrous. Many people who are co-infected would greatly benefit from 'Co-Infection Clinics', some with additional expertise in addiction. These clinics should be multidisciplinary, including knowledgeable dieticians, social workers, nurses, and psychiatric/psychosocial support. These clinics should be as accessible as possible to people living in more remote locations, as well as flexible in terms of structure (appointment only versus drop-in times). Models of coordinated, integrated care exist in the setting of HIV. These include the MAT/DOT program, Vancouver Native Health, and the Dr. Peter Center, all in Vancouver. These models should be developed and elaborated upon to include treatment and management of hepatitis C. Where possible, these clinics should incorporate other programs and services, such as meals, social activities, and educational programs.

Health Care Recommendations and Responsibilities:

- Recommendation: Existing HIV clinics should be encouraged and supported in working more collaboratively with hepatitis experts.
- Recommendation: Hepatitis experts should become more proactive in learning about and collaborating with HIV experts.

- Recommendation: All clinics should move toward integrating other health care modalities, and moving toward a holistic and patient-centered model of care.
- Recommendation: Centers for Excellence in Hepatitis C with expertise in HIV co-infection should be developed.
- Responsibility: Clinic and hospital administrators and directors, clinician scientists, other leaders in the field

- Recommendation: Health care settings should provide opportunities to see patients daily or weekly to assist them with receiving and tolerating their treatments (e.g. daily observed therapy, maximally assisted therapy). Drop-in day clinics should be developed and adapted for these purposes.
- Responsibility: Federal and provincial governments should provide sufficient financial resources to allow these types of clinics to operate. Hospitals, HIV, and hepatitis clinics should introduce this kind of flexibility and opportunity into their operations.

- Recommendation: More harm reduction and addiction treatment services must be implemented.
- Responsibility: Collaboration among Health Canada, Correctional Services Canada, harm reduction groups, provincial and regional health authorities.

Federal and Provincial Policy Issues

A plethora of policy issues were identified and discussed at the meeting. People who are HIV/HCV co-infected must first be identified as a unique population. To appropriately address the epidemic of HIV/HCV co-infection, the issue must be treated as one that is greater than the sum of its two parts. Currently people are falling through cracks everywhere, and there is a lack of expertise, research, and resources devoted to this particular problem. While moving forward on either HIV or hepatitis C will help people who are co-infected, the co-infected have a unique set of problems and issues that must be given devoted attention:

- their HIV will be much more difficult to treat because of liver disease
- their HCV will progress more rapidly and aggressively than their mono-infected counterparts, and will be more difficult to treat
- they face the stigma of both HIV and HCV
- HCV has become a huge part of HIV community-based work out of necessity, without the resources to support it.

Although there is no consensus as to whether HIV co-infection should become a part of a Hepatitis C strategy, or whether HCV co-infection should be part of an HIV strategy, or whether HIV/HCV co-infection should have its own strategy, HIV/HCV co-infection was considered by all to be a distinct problem. The federal and provincial governments must make HIV and hepatitis C co-infection a priority. There is the perpetual problem of the 'silo' mentality (each one acting as a distinctly separate government), which is why the federal and provincial governments must all be brought to the table together.

Addressing either the HIV, HCV, or HIV/HCV epidemics without addressing the social determinants of health (i.e. housing, poverty, stigma, etc.) can only ever be partially effective. Advocates and policy makers must constantly be trying to improve the social conditions that predispose people to poor health and high-risk behaviors. This includes advocating for changes to the U.S.-led 'War on Drugs', which prevents Canada from moving forward on progressive drug-related policies, including implementing harm reduction strategies.

In February, 2004, the Canadian AIDS Society produced a document entitled "A National Hepatitis C Strategy in Canada: A Discussion Paper". It is available from their website, www.cdnaids.ca. This comprehensive document should be used as a basis for further discussions.

Policy Recommendations and Responsibilities:

- Recommendation: The Canadian government should implement a national on-going hepatitis C strategy, with attached dollars, that in some significant way incorporates HIV co-infection. The CSHA should incorporate priorities regarding co-infected individuals into the strategy, with dollars attached.
- Responsibility: The Federal government must show leadership in this area, but hepatitis C and HIV community organizations and care providers must keep the pressure on the Federal government to do so. Ideally, a taskforce coalition would be

struck to move these issues forward. The Ministerial Council on HIV/AIDS should advise the federal HIV/AIDS Division to incorporate HCV co-infection, with the recommendation of attaching newly allocated dollars, into the revised CSHA.

- Recommendation: All government committees, federal or provincial, addressing HIV or hepatitis C should have significant participation from the other as part of the inherent constitution of their membership.
- Responsibility: Federal, Provincial, Territorial, and F/P/T committee chairs, as well as provincial medical association advisory bodies.

- Recommendation: Hepatitis C should be classified as an AIDS defining illness, and addiction should be classified as a disability.
- Responsibility: Provincial advocacy groups should work together to revise the definition of disability to include addiction, and Population and Public Health Branch of Health Canada (formerly LCDC) should revise their list of AIDS defining opportunistic infections to include hepatitis C.

Correctional Settings

HIV/HCV co-infection is a major issue in correctional facilities. The prevalence of hepatitis C among those who have HIV in these institutions is close to 100%. All of the problems that exist outside the prison walls, including lack of access to treatment and care, stigma and discrimination, inability and barriers to accessing harm reduction measures or addiction treatment, are magnified in correctional settings. These issues have been raised in numerous fora before, and documented in a multitude of reports. Unfortunately, little or no progress has been made towards addressing them. Poor prison conditions, such as overcrowding, make the situation worse. Sharing of rigs and needles for drug use and tattooing remains common, there is little or no preparation for inmates' release, and their re-entry into the community often results in a re-entry into a lifestyle which may put them at risk of re-infection and/or of or infecting others.

People who are in prison are good candidates for HCV treatment, if the appropriate supports are in place. It is an ideal opportunity for voluntary treatment with strong daily follow-up. This includes addiction treatment, HIV treatment, and HCV treatment. Unfortunately, prison and government officials are reluctant to admit that there is even a problem with HIV and HCV infection in prison.

Correctional Recommendations and Responsibilities:

- Recommendation: Implement existing reports regarding how correctional institutions need to change to allow for safe drug use and tattooing, methadone therapy, other addiction treatment, harm reduction, and unhindered access to knowledgeable care providers and specialists. Examples of these reports include: "Action on HIV/AIDS in Prisons: Too Little, Too Late - A Report Card", November 2002; "HIV/AIDS in Prisons: A Final Report", September 1996. Both are available at: http://www.aidslaw.ca/Maincontent/issues/prisons.htm/.

- Responsibility: Corrections Canada, provincial correctional institutions

Prevention and Education

There are many levels on which education needs to take place. Primary prevention, preventing new infections, must be achieved through the implementation of harm reduction measures (e.g. safe injection sites, prescription heroin, needle exchange programs), addiction treatment, and broad public and targeted education campaigns (towards youth, for example) regarding how HCV is transmitted and how to avoid it. There are thousands of people who don't even know they have hepatitis C because they are not considered 'high-risk'. This stereotype is dangerous, and education campaigns aimed at breaking down stereotypes and encouraging people to get tested for HCV are critical.

Secondary prevention, preventing disease progression among those already infected, can also be accomplished through the use of harm reduction and addiction treatment, in addition to appropriate community resources being developed to help people learn about the ways they can take care of their health (e.g. accessing treatment and care, reducing alcohol intake, weight loss if necessary, nutritional issues, etc.). Education for people who are co-infected also needs to include life-skills training (e.g. literacy), and lifestyle stabilization. People who are co-infected have particular needs in terms of education, particularly treatment education, because the medical issues they are dealing with are far more complex and more urgent than those of people who are HCV mono-infected.

It was agreed by all at the meeting that a lot of education needs to happen at the level of care professionals, including physicians. Most of HIV specialists know little about HCV, and vice versa. General practitioners tend not to know much about either, and especially not the combined effects of HIV and HCV. This lack of knowledge and understanding has a lot to do with why people who are co-infected fall through the cracks of care and treatment.

A major barrier to accomplishing any and all of this is the lack of national or provincial strategies to address HCV in general. Without a formal strategy, the financial resources and infrastructure are simply not present to allow for the assignment of responsibility and support of educational initiatives.

HIV is widely associated with social stigma and discrimination. Infection with the virus itself and the behaviors and lifestyles that are assumed to accompany it are all considered taboo and socially and culturally unacceptable. Because hepatitis C shares many of the same risk factors as HIV, it too has become a disease of stigma and discrimination: and brings up issues of homophobia, drug-phobia, and HIV phobia. Stigma can prevent people from getting tested, and it can prevent people from seeking treatment. There was a consensus among participants at the meeting that stigma is one of the major barriers for HIV/HCV co-infected people accessing good care, treatment, and support.

Prevention and Education Recommendations and Responsibilities:

- Recommendation: General and targeted education campaigns aimed at increasing the number of people getting tested for both viruses, and at decreasing the stigma associated with having them.
- Responsibility: Health Canada should lead and fund these initiatives, in collaboration with grassroots organizations.

- Recommendation: Continuing Medical Education programs should be developed specifically to train physicians on co-infection, and more training should be developed and offered to front-line workers. Mentorship and training programs in co-infection for physicians and researchers would be instrumental.
- Responsibility: Medical associations, leading clinicians in the field, conference organizers, and community-based organizations.

- Recommendation: HCV specific funding should be incorporated as part of the Canadian Strategy on HIV/AIDS, and used in part towards developing educational materials and resources; AIDS Service Organizations should continue to make hepatitis C co-infection a priority in their workplans.
- Responsibility: Health Canada, AIDS Service organizations and community-based organizations.

Support Needs

Many co-infected people have an increased need for social and mental health support. Both HIV and HCV can cause cognitive impairments, and HCV treatments are especially known to cause depression, anxiety, and suicidal thoughts or actions. Many co-infected people have increased fatigue, and reduced quality of life. Many also have a constellation of special needs that arise from poverty, addiction, and mental health issues that may have been present prior to infection, and from disenfranchisement in general.

There are models of peer-empowerment programs that work, such as the Vancouver Area Network of Drug Users (VANDU), and the BC Persons with AIDS Society. These models should be supported, developed, and used as a basis for developing other programs. There are currently few, if any, hepatitis C community resources, because of the lack of funding or strategy by the provincial or federal governments. Therefore AIDS Service Organizations and HIV specific community-based programs bear the huge burden oftrying to cope with the epidemic of HCV and HCV/HIV co-infection. ASOs need to find ways of being more responsive to the needs of the HCV-co-infected, including educating staff and volunteers about HCV, and becoming more flexible in their hours of operation, locations, and program delivery.

Support Recommendations and Responsibilities:

- Recommendation: Fund AIDS Service Organizations and community-based organizations to provide resources and materials to co-infected individuals.
- Responsibility: Health Canada, Provincial governments, community-based organizations

- Recommendation: Develop peer-driven networks and groups to foster mutual support and collective action for co-infected individuals.
- Responsibility: People living with HIV and hepatitis C.

- Recommendation: Develop more drop-in centers for persons co-infected, including explicit supports for people on treatment.
- Responsibility: Community-based organizations, government funders, community clinics.

Summary of Key Recommendations

Clinical Recommendations:

- **Recommendation #1**: The use of Growth Factors should be considered a standard part of the cost of treating hepatitis C. Public and private payers need to be educated about the importance of growth factors for patients. Pharmaeconomic studies should be performed to show the cost-effectiveness of these supportive treatments. Public payers should negotiate with the companies that make hepatitis C treatments, and those that make the growth factors, to enable their combined usage at a reduced cost.
- **Recommendation #2**: Public payers must be pushed into expanding their eligibility criteria for accessing and remaining on hepatitis C treatment for as long as patient and physician believe it necessary and appropriate.
- **Recommendation #3**: Identify best practices and standards of care elsewhere in the world regarding the treatment and management of HIV/HCV co-infection.
- **Recommendation #4**: Identify what specialized services, in terms of HCV treatment and co-infection , are available in Canada, and where they are available.
- **Recommendation #5**: Regularly revise treatment and management guidelines based on current evidence, and disseminate widely to physicians and patients.

Transplantation Recommendations:

- **Recommendation #1**: Provinces need to develop appropriate guidelines for the transplantation of HIV-infected individuals.

Research Recommendations:

- **Recommendation #1**: A research agenda should be developed to identify priorities in understanding the natural history of hepatitis C in the presence of HIV, new targets for drug development, and improvements in the currently available treatments.
- **Recommendation #2**: More money should be devoted to researching clinical aspects of co-infection, including natural history and pathogenesis issues.
- **Recommendation #3**: Create a network of databases for sharing (anonymized) data regarding treatment outcomes among co-infected, and a network of physicians and researchers focussing on co-infection

Health Care Recommendations:

- **Recommendation #1**: Existing HIV clinics should be encouraged and supported in working more collaboratively with hepatitis experts.
- **Recommendation #2**: Hepatitis experts should become more proactive in learning about and collaborating with HIV experts.
- **Recommendation #3:** All clinics should move toward integrating other health care modalities, and moving toward a holistic and patient-centered model of care.
- **Recommendation #4**: Centers for Excellence in Hepatitis C with expertise in HIV co-infection should be developed.
- **Recommendation #5**: Health care settings should provide opportunities to see patients daily or weekly to assist them with receiving and tolerating their treatments (e.g. daily observed therapy, maximally assisted therapy). Drop-in day clinics should be developed and adapted for these purposes.

- **Recommendation #6**: More harm reduction and addiction treatment services must be implemented.

Policy Recommendations:
- **Recommendation #1**: The Canadian government should implement a national on-going hepatitis C strategy, with attached dollars, that in some significant way incorporates HIV co-infection. The CSHA should incorporate priorities regarding co-infected individuals into the strategy, with dollars attached.
- **Recommendation #2**: All government committees, federal or provincial, addressing HIV or hepatitis C should have significant participation from the other as part of the inherent constitution of their membership.
- **Recommendation #3**: Hepatitis C should be classified as an AIDS defining illness, and addiction should be classified as a disability where it is not already.

Correctional Recommendations:
- **Recommendation #1**: Implement existing reports regarding how correctional institutions need to change to allow for safe drug use and tattooing, methadone therapy, other addiction treatment, harm reduction, and unhindered access to knowledgeable care providers and specialists.

Prevention and Education Recommendations:
- **Recommendation #1**: General and targeted education campaigns aimed at increasing the number of people getting tested for both viruses, and at decreasing the stigma associated with having them.
- **Recommendation #2**: Continuing Medical Education programs should be developed specifically to train physicians on co-infection, and more training should be developed and offered to front-line workers. Mentorship and training programs in co-infection for physicians and researchers would be instrumental.
- **Recommendation #3**: HCV specific funding should be incorporated as part of the CSHA, and used in part towards developing educational materials and resources; AIDS Service Organizations should continue to make hepatitis C co-infection a priority in their workplans.

Support Recommendations:
- **Recommendation #1**: Fund AIDS Service Organizations and community-based organizations to provide resources and materials to co-infected individuals.
- **Recommendation #2**: Develop peer-driven networks and groups to foster mutual support and collective action for co-infected individuals.
- **Recommendation #3**: Develop more drop-in centers for persons co-infected, including explicit supports for people on treatment.

National Stakeholders Meeting on Improving Access to Care, Treatment, and Support for People Living with HIV and Hepatitis C Co-infection

Friday, January 23, 2004
Crowne Plaza Hotel, Montreal, Quebec

PARTICIPANT LIST

Alex (Andy) Aitken	Quebec	Canadian Hepatitis C Network (CHCN)
Chantale Perron	Montreal	
Charles A. Altman	Montreal	AIDS Community Care Montreal (ACCM)
David McCombs	Montreal	ACCM
Dr Jenny Heathcote	Toronto	Physician
Dr. David Wong	Toronto	Physician
Dr. Jane Buxton	Vancouver	Physician
Dr. John Farley	Vancouver	Physician
Dr. Mario Ostrowski	Toronto	Physician
Dr. Mary Anne Cooper	Toronto	Physician
Dr. Patrice Junod	Montreal	Abbott Laboratories
Dr. Peter Ford	Kingston	Physician
Dr. Stuart Rosser	Winnipeg	Physician
Dr. Wendy Wobeser	Kingston	Physician
Durhane Wong-Reiger	Toronto	Anemia Institute
Erick Shields	Montreal	Schering Canada
James Kreppner	Toronto	CTAC/CHS
Jeff Potts	Ottawa	Health Canada-Hepatitis C Unit
Jennifer Gold	Montreal	Canadian HIV/AIDS Legal Network
Jennifer Lynch	Montreal	Schering Canada
John Plater	Toronto	Canadian Hemophilia Society (CHS)
Karina Pourreaux for Dr. Richard Lalonde	Montreal	Physician's office
Ken Thomson	Kelowna	Hep C Collaborative Circle
Leigh Funston	Mississauga	Hoffmann-La Roche
Lorne Fox	Montreal	Shire BioChem
Louise Binder	Toronto	Canadian Treatment Action Council (CTAC)

Lynne Belle-Isle	Ottawa	CAS
Malsah	Vancouver	British Columbia Persons with AIDS Society (BCPWA)
Marie Prévost	Montreal	Abbott Laboratories
Mel Hennan	Vancouver	Vancouver Area Network of Drug Users (VANDU)
Paul LaPierre	Ottawa	Canadian AIDS Society (CAS)
Paula Braitstein	Vancouver	CTAC/BCPWA
Phil Lundrigan	Newfoundland	CTAC
Randy Steffan	Ottawa	Schering Canada
Renaud Laporte	Montreal	Schering Canada
Robert Friday	Ottawa	Canadian Aboriginal AIDS Network
Ron Rosenes	Toronto	CTAC/ AIDS Action Now!
Rosemary Church		Pfizer Canada
Ruth Pritchard	Montreal	Bristol-Myers Squibb
Sheena Sargeant	Vancouver	Ministerial Council on HIV/AIDS
Susan Redgrave	Burlington	Pfizer Canada
Syrus Marcus Ware	Toronto	Prisoners with HIV/AIDS Support Action Network (PASAN)
Terry Pigeon	Montreal	

‘Availability of Treatments by Province & Territory for Hepatitis C’

Province	**Date of information**	**Rebetron (combo)** **Ifn-alpa2b+ribavirin** **Schering**	**Pegetron (combo)** **Peg-ifn2b+ribavirin** **Schering**	**Pegasys (mono)** **Peg-ifn2a** **Roche**	**Pegasys/Copegus** **Peg-ifn2a + ribavirin** **Roche** **(Interm CDR)**	**Particulars/Comments**
BC	Jan. 04	Special authorization, Geno. 2/3 -24 wks.	Special authorization, TN (treatment naïve), Geno. 2/3 -24 wks.	Under review	Health Canada NOC approval applied for in Aug/02-still waiting despite ‘fast track’ process. Not submitted to province yet.	ALT 1.5x normal, 2x over 6 mos.
AB	Sept. 03	Special authorization	Special authorization Unitron also available	Under review	Not submitted yet	Anti-HCV, HCV-PCR, ALT/AST or biopsy results. Provincial drug plan has no premiums for over 65
Sask	Sept. 03	Exception Drug Status (EDS)	EDS, Unitron also available	Under review	Not submitted yet	Coverage for 6 mo. w/ potential 2 more 6 mo. periods of coverage
MB	Sept. 03	EDS	Part 3 EDS Doctor must be ID’d by MB gov’t as familiar with treating HCV	Under review	Not covered	Dr. must provide genotype, ALT, biopsy, viral load, previous tx
ON	Oct. 03	Written, Physician, Section 8	Written, Physician, Section 8	Written, Physician, Section 8 *	Not submitted yet	Member TDP, Pay 4% household net income up front
PQ	Mar. 04	Up to 48 wks. Genotype 2/3 -24 wks.	Up to 48 wks. Genotype 2/3 -24 wks.	Under review		

NB/PEI				Under review		Same as Nova Scotia?
NS	Nov. 03		TN, Specialist written request	Under review	Not submitted yet	
NL	Aug. 03	Written/ph./fax request from infectious disease specialist	Written/ph./fax request from infectious disease specialist	Under review		
Yu	Aug. 03	Special authorization	Special authorization, TN	Under review	Not submitted yet	ALT 1.5x normal, 2x over 6 mos.
NWT				Under review		
Nu	Aug. 03			Under review		Paid for on a pre-approval basis depending on the policies in place in the larger jurisdictions.
FNIB				Covered (Individual approval)		

More copies of this pamphlet can be downloaded from: **www.hepcure.ca**

REBETRON ® Combo (interferon alfa-2b + ribavirin/Schering Corporation)

UNITRON (R)**Monotherapy** (peginterferon alfa-2b/Schering Corporation) **PEG** (TM)or **PEG INTRON** in the USA.

PEGETRON (TM) **Combo** (peginterferon alfa-2b + ribavirin/Schering Corporation) in the USA is **REBETOL** (R)

PEGASYS Monotherapy (peginterferon alfa-2a/Hoffmann-La Roche, Inc.) in Canada

COPEGUS (Roche ribavirin**)** is awaiting approval in Canada.

***Ribavirin may be available under Roche's Ribavirin Access Program (RAP)**

Phyllis Chuly
Acting Executive Director
BC PharmaCare
PO Box 9655 Stn Prov Govt
Victoria, British Columbia
V8W 9P2

September 14, 2003

Dear Ms. Chuly,

We were very pleased that Pharmacare and the Minister of Health announced its decision on June 12, 2003, to provide Pegetron to persons infected with hepatitis C in British Columbia. As you know, BC was the last province in Canada to make this drug available to patients, in spite of its substantially enhanced efficacy over the previously available Rebetron.

We were, however, alarmed by the criteria which have been set for accessing this drug. It is our understanding that the inclusion and exclusion criteria for accessing Pegetron are as follows:

Inclusion Criteria
- hepatitis C treatment naïve
- ALT >1.5 ULN on two consecutive occasions at least 3 months apart
- GT 1, 4, 5, 6: >2 log reduction in HCV RNA by week 14 (if yes, additional 34 weeks coverage)
- GT 2, 3: maximum period of coverage is 24 weeks

Exclusion Criteria
- aged less than 18 years
- decompensated liver disease
- active alcohol abuse
- higher risk of non-compliance
- pregnancy or lack of appropriate contraception
- illicit IV drug and/or intranasal cocaine use

Our primary concern is that these criteria are not based on currently available scientific evidence from the medical literature.

For your convenience, we are providing an outline of the evidence that we hope will provide the basis upon which the criteria will be changed. As they are, the criteria place undue and unnecessary limitations on accessing what for many may be a life-saving drug.

Treatment Naïve

This criteria is presumably based on the thinking that people who have tried and failed previous hepatitis C treatment stand little chance of succeeding with Pegetron. However, the evidence clearly indicates that the issue is not nearly so simple.

Not all people who have taken hepatitis C treatment and have not achieved a sustained virologic response (SVR – what is considered the gold standard of success of Hepatitis C treatment) are alike. There are non-responders (people whose virus didn't respond to treatment), relapsers (people whose virus did respond but once treatment ended the virus came back), and breakthroughs (people whose virus responded but came back while still on treatment). These groups have very different response rates upon re-treatment, contingent on a variety of factors, including what they were initially treated with [1].

Non-Responders:

Within non-responders, there are the people whose virus didn't respond at all to therapy, and there are those whose virus decreased at least two logs but remained detectable. The latter group may have significant improvements in their ALT and hepatic histology; they may also have improved response to more efficacious treatment [2, 3].

Most data on the re-treatment of non-responders is based on standard interferon (IFN) treatment (with or without ribavirin). Whether people took interferon monotherapy or Rebetron (i.e. combination interferon and ribavirin) has a significant impact as to whether their virus will respond to pegylated interferon [1].

Among non-responding people who were *re-treated with regular interferon* (IFN) and ribavirin (RBV):

- From meta-analyses, it was found that *among non-responders to IFN mono-therapy* when retreated with IFN+RBV, 26-32% became HCV RNA negative, and an average of 15% achieved a SVR [1].

When re-treated with pegylated interferon plus ribavirin:

- A study of 17 non-responders to IFN-monotherapy and 84 non-responders to IFN+RBV, all having genotype (GT) 1, found 25-40% of people achieved a SVR with PEG+RBV (only 10-11% among people who had previously not responded to IFN+RBV) [4]
- In a study of 212 non-responders to either IFN-mono or IFN/RBV combination, retreated with PEG+RBV, all with advanced fibrosis or

cirrhosis, and 88% GT1: among IFN-monotherapy non-responders, 53% responded to re-treatment, and 34% achieved a SVR; among non-responders to IFN/RBV, 30% became HCV RNA negative, and 11% achieved a SVR. SVR occurred in 15% of patients with GT1, and 60% of GT2/3. Only 11% of African-Americans became HCV RNA negative during retreatment, none achieved SVR [5].

Presentations at Digestive Disease Week 2003:

- Among 219 individuals, some IFN-monotherapy non-responders, some IFN/RBV non-responders; some IFN/RBV relapsers; SVR for relapsers was 42%, for combination therapy non-responders, 8%; for mono-therapy non-responders, 21% [6]
- Non-responders re-treated with Peg+RBV [6],
  - SVR in all GT: 15%
  - SVR in GT1: 5-9%
  - SVR in GT 2/3: 13-25%
- In an on-going study of 439 non responders to IFN with or without RBV, the end of treatment response (ETR) so far is 46% and SVR was 33%; SVR higher in GT-non 1 and those who previously failed IFN monotherapy; SVR in GT1 pre-treated with IFN/RBV was 15% [7]
- Among 193 non-responders to IFN+RBV, treated with PEG+RBV, there were improvements in inflammation (as measured by HAI), but not fibrosis (most improvements seen in those who became HCV RNA negative); SVR was 9% [8]
- Brazilian study presented at the Annual meeting of the European Association for the Study of the Liver (2003) found that among 131 individuals who had been treated for at least 6 mths with Rebetron found upon treatment with PEG/RBV at 24 weeks, 89% of relapsers and 67% of non-responders became HCV RNA negative, and after 48 weeks of treatment, 80% of relapsers and 58% of non-responders were HCV RNA negative [9].

Relapsers:

- *Re-treated with IFN mono vs. IFN/RBV for 24 weeks* [10]
  - 49% of relapsers treated with IFN mono became HCV RNA negative, and 5% had SVR
  - 82% of relapsers treated with IFN/RBV became HCV RNA negative, and 47% achieved SVR
- *Re-treated with PEG/RBV* [4]*:*
  - 87% achieved EOT response, and 60% SVR

ALT Levels:

One of the key criteria for accessing Pegetron is persistently elevated ALT levels. ALT levels are well known to be poor correlates of disease progression [11]. Based on a study of 867 patients, among those with persistently normal ALT values, 65% had a METAVIR score of at least F1, indicating at least some liver fibrosis (PPV=99%, NPV=35%) [12]. Furthermore, factors that may affect ALT levels are HLA class, sex, and body mass index [12], all suggesting that ALT levels are a poor marker of disease. Alarmingly, reports in the community indicate that some individuals are so desperate to elevate their ALT's in order to access Pegetron that they are consuming large quantities of alcohol before having blood drawn.

It is also important to note that people with chronic hepatitis C infection are more likely to achieve a sustained virologic response if there is no fibrosis or cirrhosis [11]. This would suggest that early treatment is better, and that individuals should not wait until their liver is inflamed or diseased before taking treatment.

Stopping Rules:

It is very important for policy-makers to consider that although a sustained virologic response is the gold standard of effective hepatitis C treatment, from the patient's perspective the key issue is to a) maintain liver function, and b) to improve liver function even if there is still virus present. There are many new treatments and therapeutic vaccines for hepatitis C in development, and for patients currently infected with hepatitis C, if the goal of a sustained virologic response is not possible, then keeping one's liver functioning until there are more effective treatments available becomes the goal. There is research that indicates that in spite of a lack of virologic response, histologic response is achievable using "maintenance therapy". The concept of maintenance therapy is based on the observation that up to 40% of non-responders have a histologic response during treatment [2, 3].

In a meta-analysis examining histologic improvements following PEG/RBV treatment, Poynard et al. found [13]:

Treatment Response	Number	Fibrosis Improved	Fibrosis Stabilized	Fibrosis Worsened
Sustained	1094	25%	68%	7%

responders				
Relapsers	464	16%	67%	17%
Non-responders	1452	17%	62%	21%

Another important consideration regarding the stopping rules for Pegetron is that people co-infected with HIV may have altered HCV viral dynamics in response to HCV treatment and may therefore require a longer period to reach >2 log reduction in HCV RNA [14].

Pegetron in children:

One of the exclusion criteria is if patients are aged less than 18 years. Although data are limited on the use of pegylated interferon in children, a small study of 14 children, of whom 13 were GT1, who were all treated with PEG monotherapy, found that at 72 weeks 42% achieved a SVR. [15]

Other Exclusion Criteria:

Active alcohol abuse, higher risk of non-compliance, pregnancy or lack of appropriate contraception, illicit IV drug and/or intranasal cocaine use are all listed as exclusion criteria. However, none of these issues are defined. What constitutes alcohol abuse? What is 'appropriate contraception'? Is the illicit IV drug and/or intranasal cocaine use based on ever having used, or currently using? And while the reason behind the latter criteria is presumably to prevent re-infection, what if an individual only uses sterile paraphernalia?

Management of Ribavirin Toxicities:

An important and thus far completely neglected issue by Pharmacare in relation to treatment of hepatitis C infection, are the hematologic toxicities associated with ribavirin treatment, specifically anemia. These result in discontinuation of treatment in 10 to 14% of patients [11], and the reduction of ribavirin dose (resulting in poorer response rates) among many, many more. There are few treatments available for the treatment of ribavirin induced anemia. However, Eprex (epoetin-alfa) is a licensed glycoprotein product manufactured using recombinant DNA technology. It contains the identical amino acid sequence of isolated natural erythropoietin, and is indicated for use in patients with kidney failure, surgery patients, cancer patients (because both cancer itself and

chemotherapeutic agents can induce anemia), as well as zidovudine induced anemia in patients with HIV infection. Although not well studied in the setting of ribavirin induced anemia, a preliminary study found that 88% (vs. 60% on placebo, $p<0.001$) of patients who received the recombinant epoetin-alfa were able to maintain full dose ribavirin therapy , and that quality of life measures were much higher in the Eprex treated group compared to placebo [16].

In summary, we feel that given existing data, the criteria for accessing Pegetron in British Columbia are lacking in a number of important ways that have direct impact on patient's lives. While we understand the need to contain costs, this need must be balanced against the medical needs of people struggling against chronic hepatitis C infection. Hepatitis C treatment is not a life-long treatment. The lifetime costs, however, of chronic hepatitis C disease are substantial if one considers the costs of hospitalization, health care utilization, and transplantation. The BC Center for Disease Control has estimated that the medical costs without treatment for a person with hepatitis C, from diagnosis to death, are approximately $1 million [17]. This is compared to the approximately $11,000 for a 32-week course of Pegetron.

We strongly urge you to consider the data we have presented to you, and to conduct your own research on these issues. We are confident that you will agree that the science does not support the criteria, and we eagerly await your response.

Sincerely, on behalf of the BC HIV/Hepatitis C Co-Infection Action Coalition,

Paula Braitstein
Senior Policy Advisor on Health Promotion
BC Persons with AIDS Society

Malsah
Chair, Board of Directors
BC Persons with AIDS Society

Ken Thomson
Chairperson, Hub Team
BC Hepatitis C Collaborative Circle

Terry Howard
Coordinator, Prison Outreach Program

BC Persons with AIDS Society

Evin Jones
Executive Director
YouthCo AIDS Society

Rick Barnes
Communications Director
AIDS Vancouver

Miki Hansen
Executive Director
AIDS Vancouver Island

Ann Livingstone
Coodinator
Vancouver Area Network of Drug Users

cc.
Hon. Minister Colin Hansen, Minister of Health Services, British Columbia
Premier Gordon Campbell, British Columbia
Dr. Penny Ballem, Deputy Minister of Health, British Columbia
Lorne Mayencourt, MLA Vancouver-Burrard
Dr. Urs Steinbrecher, MD, Chair, Pharmacare Adjudication Committee
Dr. Eric Yoshida, Hepatologist
Dr. Frank Anderson, Gastroenterologist
Dr. Valentina Montessori, Infectious Disease Specialist, BC Center for Excellence in HIV/AIDS
Dr. Mel Krajden, BC Center for Disease Control
Mr. Brian Harrigan, BC Center for Excellence in HIV/AIDS

References Cited:

1. Shiffman, M., *Retreatment of patients with chronic hepatitis C.* Hepatology, 2002a. **36**: p. S128-S134.
2. Shiffman, M., *Histologic improvement in response to interferon therapy in chronic hepatitis C.* Viral Hepatitis Review, 1999. **5**: p. 27-43.
3. Shiffman, M., *et al.*, *Relationship between biochemical, virologic and histologic response during interferon treatment of chronic hepatitis C.* Hepatology, 1997. **26**: p. 780-785.
4. Jacobson, I., *Pegylated interferon alfa-2b plus ribavirin in patients with chronic C: A trial in prior non-responders to interferon monotherapy or combination therapy and in combination therapy non-responders.* Gastroenterology, 2002. **122**: p. A626.
5. Shiffman, M. *Retreatment of HCV non-responders with peginterferon and ribavirin: results from the lead-in phase of the hepatitis C antiviral long term treatment against cirrhosis (HALT-C) trial*. 2002b: Hepatology.
6. Jacobson, I., *et al. Pegylated interferon alfa-2B plus ribavirin in patients with chronic hepatitis C: a trial in prior nonresponders to interferon monotherapy or combination therapy and in combination therapy relapsers: final results*. in *Digestive Disease Week*. 2003. Orlando, Fl.
7. Gaglio, P., *et al. Treatment with pegylated interferon alfa-2B and ribavirin produces significant sustained virologic response rates in HCV infected patients who failed prior therapy*. in *Digestive Disease Week*. 2003. Orlando, Fl.
8. Selim, K., *et al. Histological Improvement in Patients with Pegylated Interferon Alpha-2b plus Ribavirin Who Were Previously Non-Responders to Rebetron*. in *Digestive Disease Week*. 2003. Orlando, Fl.: Gastroenterology.
9. Parise, E., *et al. Peginterferon alfa-2a (40KD) (Pegasys) and Ribavirin (Copegus) Therapy in Patients with Chronic Hepatitis C Who Did Not Respond to, or Relapsed After Combination Interferon alfa and Ribavirin Treatment: Preliminary Results of an Ongoing Prospective Multicenter Trial*. in *European Association of Studies of the Liver*. 2003. Geneva, Switzerland: Journal of Hepatology.
10. Davis, G., *et al.*, *Recombinant interferon alfa-2b alone or in combination with ribavirin for retreatment of interferon relapse in chronic hepatitis C.* New England Journal of Medicine, 1998. **339**: p. 1493-1499.
11. Anonymous, *National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C 2002 (June 10-12, 2002).* Gastroenterology., 2002. **123**(6): p. 2082-99.
12. Pradat, P., *et al.*, *Predictive value of ALT levels for histologic findings in chronic hepatitis C: A European Collaborative Study.* Hepatology, 2002. **36**: p. 973-977.
13. Poynard, T., *et al.*, *Impact of pegylated interferon alfa 2b and ribavirin on liver fibrosis in patients with chronic hepatitis C.* Gastroenterology, 2002. **122**(5): p. 1303-1313.

14. Kottilil, S., *et al. Early HCV kinetics predicts response to peg-interferon alpha 2B and ribavirin anti-HCV therapy among HIV co-infected individuals*. in *2nd International AIDS Society Conference on HIV Pathogenesis and Treatment*. 2003. Paris, France.
15. Schwarz, K., *et al. The safety, efficacy, and pharmacokinetics of Peginterferon Alfa-2a (40KD) in children with hepatitis C*. in *Digestive Disease Week*. 2003. Orlando, Fl.: Gastroenterology.
16. Afdhal, N., *et al. Epoetin alfa treatment of anemic HCV-infected patients allows for maintenance of ribavirin dose, increases hemoglobin levels, and improves quality of life vs. placebo: a randomized, double-blind, multicenter study*. in *Digestive Disease Week*. 2003. Orlando, Fl.: Gastroenterology.
17. BC Center for Disease Control. *A hepatitis strategy for British Columbia*, . 1999, BCCDC: Vancouver.