

## COHORT PROFILE

# Cohort Profile: The Canadian HIV–Hepatitis C Co-infection Cohort Study

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## What is the Canadian HIV–Hepatitis C Co-infection Cohort and how did the study come about?

Hepatitis C virus (HCV) has emerged as one of the most vexing health problems facing HIV-infected persons. Due largely to injection drug use (IDU), >30% of HIV-infected patients are co-infected with HCV in developed countries<sup>1,2</sup> with 10 million co-infected worldwide.<sup>3</sup> In 1999, 11 194 Canadians were estimated to be co-infected<sup>4</sup> and this number has likely increased substantially since. HCV infection has also increasingly been reported in HIV-positive men having sex with men (MSM) who have not used injection drugs.<sup>5</sup> Since the advent of highly active antiretroviral therapy (HAART) there have been dramatic reductions in morbidity and mortality from virtually all causes of illness among HIV-infected persons.<sup>6,7</sup> One of the glaring exceptions to this trend is

death from end-stage liver disease (ESLD) with rates increasing 4- to 8-fold in the post-HAART era.<sup>8–11</sup> This excess mortality may be due, in part, to improved overall survival associated with HAART, allowing competing morbidities and mortalities that were once rarely observed. In addition, HCV-associated hepatic fibrosis has been shown to progress more rapidly in the context of HIV infection,<sup>12–14</sup> likely due to immune dysfunction.<sup>15–17</sup> Several other factors may be at play, including chronic hepatotoxicity related to antiretrovirals, incomplete immune recovery, heavy alcohol use and problems with access and/or adherence to HAART and HCV treatment in a population with high rates of substance use. The growing burden of chronic HCV infection is expected to result in dramatic increases in the rates of cirrhosis, liver failure, hepatocellular carcinoma, transplant needs<sup>18</sup> and related annual healthcare costs in Canada<sup>19</sup> and worldwide.

Understanding the complex interplay between socio-demographic factors, substance use, biology and treatments that may affect outcomes in co-infection is necessary to meet the challenge of providing effective

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medical care to the growing number of HIV–HCV co-infected persons. The Canadian HIV–HCV co-infection cohort (CCC) brings together experts in HIV, infectious diseases, hepatology, immunology, public health, biostatistics and epidemiology in a translational research program that is aimed at addressing the multifaceted nature of co-infection.

In 2003 we launched a prospective pilot study in Quebec funded by the *Fonds de la recherche en santé du Québec* (FRSQ). Patients were identified from existing clinic populations at three university-based HIV clinics providing multidisciplinary team care located in Montreal, Quebec, Canada: during the pilot phase of this project we recruited 253 patients and followed them for 2 years. Data obtained were then used to estimate expected rates of exposures and outcomes for power calculations, as well as for planning and anticipating the logistics required to conduct a larger Canadian study. Furthermore, we clearly demonstrated the feasibility of maintaining a cohort study with a population of patients that is traditionally considered difficult to follow.

The cohort has now been expanded, and has recruited 950 co-infected persons from 16 sites across Canada and is funded by the Canadian Institutes of Health Research (CIHR), FRSQ and Canadian HIV Trials Network (CTN). Participating centres include university-based HIV treatment programs and community-based clinics located in both large and small urban centres across the country. A list of participating centres and their patient profiles is found in Table 1.

## How is the CCC organized?

The CCC Scientific Steering Committee (SC) is responsible for defining and prioritizing the research agenda, addressing barriers to study enrolment and retention, establishing working/writing groups, preparing data for presentation or publication and approving new study questions and new collaborations with other Canadian or international researchers. The SC membership includes the principal investigator (PI) who acts as chair, site co-investigators and two community representatives. All active sites have input and one vote in the SC irrespective of contributing data to a specific scientific aim or question. The CCC coordinating office is divided into two teams (the Analysis/Data Management team and the Project Management team), both located at the McGill University Health Center, Montreal. The Analysis/Data management team provides expertise in methodology, statistics and data management. The PI and study manager are responsible for overall project management and administration and facilitating communications between the SC, working groups and research collaborators, and communicating results to the community and funding partners.

## What does the CCC cover and who are included in the cohort?

We have recruited from a variety of HIV centres across the country in both major urban centres and smaller cities in an attempt to reflect the Canadian epidemic (Figure 1). We have specifically sought to include individuals who may be extremely marginalized (e.g. l'Equipe Mobile, a mobile care model that serves injection drug (ID) users living on the street in Montreal; Pender Clinic in Vancouver's Downtown East Side), access various models of care (specialty clinics, directly observed therapy programs, outreach programmes) and have diverse risk profiles (e.g. active and ex-ID users, MSM, women, aboriginals). There is also significant variability in the population with respect to treatment to allow for adequately powered subgroup analyses (i.e. 77% on HAART, 11% naïve, 23% with liver biopsies and 14% with exposure to HCV treatment) (Table 1). Together, the sites follow ~1930 co-infected patients of whom 950 (50%) have been recruited (Table 2).

Inclusion criteria are broad to avoid limiting current and future research questions. Eligible patients are adults aged >16 years (based on provincial law) with documented HIV infection (ELISA with western blot confirmation) and with chronic HCV infection or evidence of HCV exposure (e.g. HCV-seropositive by enzyme-linked immunosorbent assay (ELISA) with recombinant immunoblot assay II (RIBA II) or enzyme immunoassay (EIA) confirmation, or if serologically false negative, HCV–RNA-positive). All eligible patients are approached to participate to avoid selection bias. A refusal log is kept in order to assess response bias. Visits are scheduled every 6 months ( $\pm 1$  month) specifically for the study or incorporated into routine medical follow-up for a minimum of 5 years. Participants receive \$15 per visit to compensate for out-of-pocket expenses. The study has been approved by all the research ethics boards of the participating institutions and the community advisory committee (CAC) of the CTN.

## What are the primary objectives?

The primary objective of this study is to determine the effect of HAART progression to ESLD in HCV–HIV co-infection. We will evaluate the contributions of important social factors, toxicities and immunologic factors that may modify fibrosis progression rates. We will also examine the rates of chronic toxicities, specifically hepatic steatosis and insulin resistance, and its association with HAART use. We will perform a detailed immunopathogenesis substudy to assess peripheral blood and liver HCV- and HIV-specific immune responses in HAART treated vs untreated individuals. Because of the need to easily follow patients and intervene prior to the onset of ESLD, we will also develop methods for evaluating fibrosis

**Table 1** HIV/HCV cohort profile: Selected demographic and clinical features of recruited patients at participating sites in the CCC

| Sites         | <i>n</i> | Median follow-up in months (IQR) | Median age (years) | Females (%) | Aboriginals (%) | MSM (%) | Current IDU (%) | Previous IDU (%) | Liver biopsy (%) | HAART at BL (%) | Naïve at BL (%) | Exposure HCV Rx (%) |
|---------------|----------|----------------------------------|--------------------|-------------|-----------------|---------|-----------------|------------------|------------------|-----------------|-----------------|---------------------|
| MCI           | 152      | 31 (12, 51)                      | 42                 | 23          | 2               | 31      | 33              | 77               | 15               | 71              | 14              | 4                   |
| CHUM          | 167      | 7 (0, 26)                        | 44                 | 15          | 1               | 17      | 51              | 93               | 16               | 68              | 20              | 8                   |
| MGH           | 51       | 29 (9, 46)                       | 45                 | 24          | 0               | 20      | 8               | 61               | 8                | 80              | 2               | 6                   |
| Calgary       | 49       | 11 (6, 13)                       | 44                 | 28          | 23              | 21      | 7               | 84               | 21               | 91              | 2               | 16                  |
| QuartierLatin | 15       | 8 (0, 12)                        | 44                 | 0           | 0               | 20      | 50              | 90               | 20               | 80              | 10              | 20                  |
| Oak Tree      | 66       | 0 (0, 0)                         | 36                 | 86          | 44              | 19      | 23              | 95               | 14               | 79              | 5               | 14                  |
| Native health | 52       | 0 (0, 0)                         | 46                 | 48          | 37              | 22      | 63              | 100              | 4                | 74              | 7               | 0                   |
| Pender        | 85       | 0 (0, 6)                         | 45                 | 24          | 28              | 11      | 57              | 93               | 11               | 76              | 15              | 6                   |
| St Paul's     | 57       | 0 (0, 0)                         | 48                 | 6           | 12              | 41      | 12              | 65               | 35               | 82              | 6               | 12                  |
| Ottawa        | 66       | 7 (0, 12)                        | 47                 | 21          | 11              | 20      | 18              | 70               | 48               | 84              | 11              | 29                  |
| Hamilton      | 28       | 0 (0, 0)                         | 42                 | 23          | 15              | 15      | 8               | 54               | 85               | 92              | 8               | 38                  |
| Sudbury       | 60       | 5 (0, 6)                         | 46                 | 34          | 34              | 10      | 32              | 85               | 15               | 75              | 7               | 22                  |
| Sunnybrook    | 19       | 0 (0, 0)                         | 53                 | 0           | 0               | 50      | 13              | 63               | 88               | 100             | 0               | 50                  |
| Toronto       | 57       | 11 (0, 14)                       | 47                 | 13          | 4               | 71      | 10              | 42               | 44               | 87              | 8               | 37                  |
| Windsor       | 15       | 6 (0, 8)                         | 47                 | 13          | 13              | 47      | 27              | 80               | 27               | 80              | 7               | 13                  |
| Halifax       | 12       | 6 (0, 10)                        | 47                 | 17          | 0               | 17      | 8               | 75               | 67               | 83              | 8               | 42                  |
| Overall       | 950      | 6 (0, 18)                        | 45                 | 25          | 12              | 25      | 31              | 80               | 23               | 77              | 11              | 14                  |

BL: baseline; Rx: treatment; MCI: Montreal Chest Institute; CHUM: Centre Hospitalier de l'Université de Montréal. IQR = inter-quartile range; MGH = Montreal General Hospital; MSM = men having sex with men; IDU = injection drug use.



**Figure 1** Map of participating sites in the CCC study

**Table 2** Recruitment statistics for sites participating in the CCC

| Site                                   | Province | PI          | Approximate number of HIV/HCV patients followed | Number recruited as of July 2009 |
|--|----------|-------------|---|----------------------------------|
| Montreal Chest Institute <sup>a</sup>  | QC       | M.B. Klein  | 170   | 152                              |
| CHUM <sup>a</sup>                      | QC       | D. Rouleau  | 200   | 167                              |
| Montreal General Hospital <sup>a</sup> | QC       | J. Cox      | 65  | 51                               |
| Clinique du Quartier Latin             | QC       | P. Cote     | 100   | 15                               |
| Pender Clinic                          | BC       | B. Conway   | 200   | 85                               |
| St Paul's Hospital                     | BC       | J. Montaner | 200   | 57                               |
| Native Health Clinic                   | BC       | M. Tyndall  | 200   | 52                               |
| Oak Tree Clinic                        | BC       | N. Pick     | 80  | 66                               |
| Calgary                                | AB       | J. Gill     | 80  | 49                               |
| Sudbury                                | ON       | R. Sandre   | 80  | 60                               |
| Hamilton                               | ON       | H. Shariq   | 100   | 29                               |
| Toronto                                | ON       | S. Walmsley | 100   | 56                               |
| Windsor                                | ON       | J. Cohen    | 40  | 15                               |
| Ottawa                                 | ON       | C. Cooper   | 200   | 66                               |
| Sunnybrook                             | ON       | A. Rachlis  | 55  | 19                               |
| Halifax                                | NS       | D. Haase    | 60  | 12                               |
| Total                                  | 16       |             | 1930  | 950                              |

QC: Quebec; BC: British Columbia; AB: Alberta; ON: Ontario; NS: Nova Scotia.

<sup>a</sup>Centres participating in the pilot phase. These centres continue to recruit and follow patients in the expanded study.

progression rates in co-infection and validate non-invasive markers for predicting fibrosis progression comparing their performance with rates obtained from single and serial liver biopsies/clinical outcomes.

Our long-term aims are to investigate means of slowing liver disease progression rates in co-infection. In particular, we will evaluate of the role of HCV treatment in the evolution of liver disease with a particular emphasis on evaluating access to treatment, predictors of response and comparing responders vs non-responders. The cohort will serve as a research network for additional questions important to understanding co-infection and related health outcomes. A cross-disciplinary approach is encouraged by engaging a variety of researchers (i.e. virology, psychiatry, health services, etc.).

## What has been measured?

Socio-demographic, medical, behavioural and quality of life information is collected using questionnaires. The questionnaire consists of 102 multiple-choice questions and 11 short answers divided into nine sections: demographics, risk factors, drug use history, smoking and drinking habits, hepatitis data, HIV data, treatment information, clinical and laboratory data. The questionnaires were developed in consultation with local medical specialists (HIV and HCV), epidemiologists and clinical research coordinators. The instrument was also inspired by existing questionnaires used with injection drugs users<sup>20,21</sup> and alcohol intake is assessed based on the Veterans Aging Cohort Study.<sup>22</sup> The EQ-5D questionnaire is used to assess quality of life.<sup>23</sup> The questionnaire was piloted initially among 20 patients in English and French, and subsequently refined. In the pilot phase all items on the questionnaires had a high level of completion with a maximum of 5% missing for any data element.

Baseline evaluations are aimed at obtaining demographic information, risk factor and behavioural information, establishing diagnoses and reviewing other medical conditions that may impact on liver function (i.e. HBV infection, alcohol, iron overload, autoimmune disease, medications, etc.) Follow-up evaluations update information on risk behaviours, medical treatments and diagnoses. Body mass index, blood pressure and waist circumference are recorded at each visit.

At each visit the following blood tests are performed [except where indicated by (†), which are performed at baseline only].

- (i) Liver profile (ALT, AST, GGT, alkaline phosphatase, total bilirubin, albumin, PT/PTT/INR).
- (ii) Complete blood count, biochemistry and fasting lipid profile.
- (iii) Fasting glucose and insulin.
- (iv) Serum alpha-feto protein, cryoglobulin levels<sup>†</sup>.

- (v) Autoimmune markers (e.g. ANA, immunoglobulins)<sup>†</sup>.
- (vi) Hepatitis A and B serology (if not documented within 1 year of study entry).
- (vii) Serum ferritin<sup>†</sup>.
- (viii) TSH.
- (ix) Plasma HIV RNA.
- (x) Absolute and relative CD4, CD8 T-cell counts.
- (xi) Plasma HCV RNA (qualitative and if positive, quantitative<sup>†</sup>).
- (xii) HCV genotype<sup>†</sup>.

Plasma, serum and peripheral blood mononuclear cell (PBMC) samples are obtained, frozen and stored. Liver biopsy samples are banked when performed as part of clinical care.

## What are the recruitment and attrition rates?

As of July 2009, 950 patients have been recruited from 16 centres with an average follow-up time of 6 months (IQR 0, 18). There have been 33 deaths and 15 withdrawals from the study. Despite the social barriers faced by our participants, only 32 (3%) have been lost to follow-up (defined as missing more than 2 visits).

## How are the data collected and managed?

A unique identifier is assigned to each participant, which that encodes information that can be used to non-nominally identify subjects who may have moved to one of the other sites. Participating subjects may complete questionnaires alone or with the aid of the research nurse. Supplementary information is then abstracted from medical records and laboratory reports by the research personnel. Questionnaires are then mailed to coordinating office every 3 months and scanned/verified into a password protected computerized database (Teleform<sup>®</sup> software). All data are handled confidentially.

PBMCs, plasma and serum are collected using standard isolation techniques, aliquoted, frozen and stored. All samples are logged using non-nominal identifiers and if not used will be destroyed after 15 years. The purpose of sample collection is to perform tests that will enable the study of biologic variables associated with clinical outcomes and responses to therapy in dual infection. These may include, but are not limited to, isolation of HCV and HIV virus (e.g. for quantification, genotyping, evaluation of viral quasispecies), measurement of immune responses to both viruses (e.g. cytotoxic T-lymphocyte assays, cytokines) and evaluation of host factors associated with clinical course (e.g. HLA typing). Additional testing on these samples may occur

as new technologies are developed for the study of chronic immune and viral diseases.

Clinical endpoints and deaths are carefully collected and reviewed. Detailed information on causes of death is collected using the Coding of Death in HIV (CoDe) system.<sup>24</sup> Sites are also asked to link to provincial vital statistics bureaus to determine precise causes of death in patients known to have died and to determine whether patients lost to follow-up are deceased. ESLD diagnoses are verified using structured data collection forms. An endpoints team is in charge of reviewing endpoints and adjudicating in cases where an outcome is uncertain.

The CCC data management/analysis team will address the primary research questions using data from all the sites. Analyses and publications or presentations resulting from these analyses will be developed by writing committees formed by the SC. Any of the CCC investigators may propose secondary analyses unrelated to primary research objectives and each site may choose to take part or not in a given study. Substudies or specific data analyses using the national data are reviewed by the SC through concept sheets available on the CCC website. To ensure judicious use of specimens that may be in limited supply, use of specimens requires prior approval by the SC. Ethics approval to conduct the specific research with the specimens must be documented prior to release of specimens and a material transfer agreement must be signed.

## Knowledge translation and dissemination

The CCC has an interactive website (<http://www.ctnforums.org/networks>) to facilitate the transfer of information to CCC investigators through a password-protected administrative website that includes all study materials, working group specific bulletin boards, meeting and teleconference agendas and minutes and a secure location for posting concept sheets and manuscripts.

### Twice-yearly meetings

The conjunction with the CTN, two face-to-face investigators meetings are held in various locations across Canada each year. In addition, teleconferences are conducted as needed.

The public can access the CCC Cohort website (<http://www.cocostudy.ca>) to receive updates on the study's progress, research findings and process for collaborating.

We will share our research findings through presentation at national and international scientific meetings, to community organizations and through publication in scientific and lay media.

## What has been found? Key findings and publications

Using data from the CCC, we have demonstrated that a simple model, the AST-to-platelet ratio index (APRI), is highly predictive of significant fibrosis in HIV/HCV co-infection.<sup>25</sup> We subsequently evaluated the evolution of the APRI, determined its predictive value for hepatic outcomes and assessed the effect of HAART on the progression rate of liver fibrosis, the first longitudinal study on this question.<sup>26,27</sup> In addition, we have recently completed the primary analysis of the pilot project and reported that persons living with HIV-HCV co-infection in Montreal experience unstable and at-risk lifestyles that impact treatment success and lead to very high rates of mortality (18 times that of age-matched Quebec population) and ESLD even in the short term.<sup>28</sup> These findings highlight that interventions aimed at improving social circumstances, reducing drug use and at increasing the delivery of HCV treatment in particular, will be necessary to improve health outcomes in this population.

## What are the main strengths and weaknesses?

Although other co-infection cohorts exist,<sup>29–33</sup> the majority involve ID users exclusively or are single-centre HCV treatment cohorts. The CCC represents one of the largest and most diverse prospective cohorts of co-infected persons in terms of its composition of participants and investigators. Our large sample size, comprehensive and long-term follow-up will enable us to determine with precision the rate of liver progression in HAART exposed vs unexposed patients. All observational research faces challenges in a large part due to the non-random allocation of treatments. Although we will make careful ascertainment of covariates to control for important potential confounders, try to be as inclusive as possible and will employ sophisticated analysis strategies to minimize biases, we may not be able to completely avoid all pitfalls. Certainly losses to follow-up and missing data will occur but we have demonstrated that this can be minimized even in this patient population. Our study is restricted to patients receiving HIV care, thus may not fully represent the experience of the wider co-infected population, who may not be accessing medical care regularly. We anticipate the possibility that fewer outcomes will be observed than predicted, despite our preliminary findings, especially if over the course of the study new HAART regimens become more effective and less hepatotoxic or more patients are successfully treated for HCV. Although these interventions are on the horizon, their incorporation into routine clinical practice will likely take longer than this initial study period. We will, however,

monitor event rates and adjust our research plan if necessary. We feel confident that our data collection and design will allow us to redirect the study to focus on a myriad of other important questions should this become a problem.

## How can I collaborate? Where can I find out more?

We encourage the participation of other interested investigators and especially graduate students at participating institutions to collaborate (see website above).

### Process for adding new sites

As the CCC evolves, it is anticipated that new sites may be invited to participate to expand the geographic and population representation in the cohort. New sites must be Canadian and agree to abide by the principles of collaboration. Addition of new sites will require SC approval. For further information they should contact the CCC study manager.

### Process for outside collaborators

We encourage national and international collaborators who are not members of the CCC to be involved in data and/or laboratory analyses. Collaborating scientists will be encouraged to raise relevant scientific questions beyond the data analysis as contracted by the CCC; however, these requests for approval for data analysis, presentation or publication must follow the principles outlined in the policies above. These collaborators will be required to acknowledge that CCC data and specimens are the property of the CCC.

## Conclusions

Our study will not only provide important information on the evolution of co-infection in Canada but will also broaden the understanding of the immunopathogenesis of HCV infection and the roles HIV and HAART play in the development of liver disease through the conduct of specific substudies. Furthermore, our study should provide important insights into the relative contributions of other factors that may modify disease progression thus allowing targeted health interventions which may benefit co-infected persons. Clearly the richness of the data acquired and the expertise of the investigators assembled through this cohort will permit in-depth studies of many additional aspects of co-infection. We will also be well positioned to address the social determinants of health outcomes, make comparisons

between models of care and evaluate quality of life issues, and thus contribute knowledge that will be essential for managing this complex condition. We have therefore provided a mechanism whereby additional projects may be assessed and undertaken by members of the SC or outside collaborators interested in this growing epidemic with the goal of improving the care and treatment of co-infected persons worldwide.

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**Conflict of interest:** None declared.

## References

- Public Health Agency of Canada. *HIV/AIDS Epi Updates (May 2005)*. <http://www.phac-aspx.gc.ca/publicat/epi-u-aepi/epi-05/index-eng.php> (2 September 2009, date last accessed).
- World Health Organization. *Fact Sheet No. 164. Hepatitis C 2000*. <http://www.who.int/mediacentre/factsheets/fs164/en> (13 July 2009, date last accessed).
- World Health Organization. *HIV/HCV Co-infection 2006*. [http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050411\\_7](http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050411_7) (13 July 2009, date last accessed).
- Remis RS. *A Study to Characterize the epidemiology of hepatitis C Infection in Canada*. <http://www.phac-aspc.gc.ca/hepe/pubs/hivhcv-vhevih/> (2 September 2009, date last accessed).
- Brejt N, Gilleece Y, Fisher M. Acute hepatitis C: changing epidemiology and association with HIV infection. *J HIV Ther* 2007;**12**:3–6.
- Wright TL, Hollander H, Pu X *et al*. Hepatitis C in HIV-infected patients with and without AIDS: prevalence and

- relationship to patient survival. *Hepatology* 1994;**20**: 1152–55.
- <sup>7</sup> Hogg RS, Yip B, Kully C, Craib KJ *et al.* Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *Cmaj* 1999;**160**:659–65.
  - <sup>8</sup> Bica I, McGovern B, Dhar R *et al.* Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001;**32**: 492–97.
  - <sup>9</sup> Macias J, Melguizo I, Fernandez-Rivera FJ *et al.* Mortality due to liver failure and impact on survival of hepatitis virus infections in HIV-infected patients receiving potent antiretroviral therapy. *Eur J Clin Microbiol Infect Dis* 2002; **21**:775–81.
  - <sup>10</sup> Lewden C, May T, Rosenthal E *et al.* Changes in causes of death among adults infected by HIV between 2000 and 2005: the "Mortalite 2000 and 2005" surveys (ANRS EN19 and Mortavic). *J Acquir Immune Defic Syndr* 2008;**48**: 590–98.
  - <sup>11</sup> Rosenthal E, Pialoux G, Bernard N *et al.* Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study). *J Viral Hepat* 2007;**14**:183–88.
  - <sup>12</sup> Graham CS, Baden LR, Yu E *et al.* Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; **33**:562–69.
  - <sup>13</sup> Sanchez-Quijano A, Andreu J, Gavilan F *et al.* Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. *Eur J Clin Microbiol Infect Dis* 1995;**14**:949–53.
  - <sup>14</sup> Soto B, Sanchez-Quijano A, Rodrigo L *et al.* Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997;**26**:1–5.
  - <sup>15</sup> Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. *Blood* 1994;**84**:1020–23.
  - <sup>16</sup> Puoti M, Bonacini M, Spinetti A *et al.* Liver fibrosis progression is related to CD4 cell depletion in patients coinfecting with hepatitis C virus and human immunodeficiency virus. *J Infect Dis* 2001;**183**:134–37.
  - <sup>17</sup> Rockstroh JK, Spengler U, Sudhop T *et al.* Immunosuppression may lead to progression of hepatitis C virus-associated liver disease in hemophiliacs coinfecting with HIV. *Am J Gastroenterol* 1996;**91**:2563–68.
  - <sup>18</sup> Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000;**90**: 1562–69.
  - <sup>19</sup> El Saadany S, Coyle D, Giulivi A, Afzal M. Economic burden of hepatitis C in Canada and the potential impact of prevention Results from a disease model. *Eur J Health Econ* 2005; [Epub 11 March 2005].
  - <sup>20</sup> Hankins C, Alary M, Parent R, Blanchette C, Claessens C. Continuing HIV transmission among injection drug users in Eastern Central Canada: The SurvUDI Study, 1995 to 2000. *J Acquir Immune Defic Syndr* 2002;**30**:514–21.
  - <sup>21</sup> Roy E, Haley N, Leclerc P, Cedras L, Blais L, Boivin JF. Drug injection among street youths in Montreal: predictors of initiation. *J Urban Health* 2003;**80**:92–105.
  - <sup>22</sup> Justice AC, Dombrowski E, Conigliaro J *et al.* Veterans Aging Cohort Study (VACS): Overview and description. *Med Care* 2006;**44** (8 Suppl 2):S13–24.
  - <sup>23</sup> Miners AH, Sabin CA, Mocroft A, Youle M, Fisher M, Johnson M. Health-related quality of life in individuals infected with HIV in the era of HAART. *HIV Clin Trials* 2001;**2**:484–92.
  - <sup>24</sup> Coding of Death in HIV (CoDe) System. <http://www.cphiv.dk/CoDe/tabid/55/Default.aspx> (13 July 2009, date last accessed).
  - <sup>25</sup> Al-Mohri H, Cooper C, Murphy T, Klein MB. Validation of a simple model for predicting liver fibrosis in HIV/hepatitis C virus-coinfected patients. *HIV Med* 2005;**6**: 375–78.
  - <sup>26</sup> Al-Mohri H, Murphy T, Lu Y, Lalonde RG, Klein MB. Evaluating liver fibrosis progression and the impact of antiretroviral therapy in HIV and hepatitis C coinfection using a noninvasive marker. *J Acquir Immune Defic Syndr* 2007;**44**:463–69.
  - <sup>27</sup> Klein MB A-MH, Murphy T, Kato C, Rouleau D. Contribution of drug use and lifestyle to hepatic fibrosis in HIV–HCV coinfection In: *Proceedings of the 13th Conference on Retroviruses and Opportunistic Infections*. Denver, Colorado, 2006.
  - <sup>28</sup> Klein MB RD, Cox J, Saeed S, Murphy T. Canadian Co-Infection Cohort Study A detailed profile of HIV-Hepatitis C Virus (HCV) co-infected persons receiving care in Montreal: The Canadian HIV-Hepatitis C Cohort Pilot Study. In: *Proceedings of the 17th Annual Conference on HIV/AIDS Research*. Montreal, Quebec, Canada, 2008.
  - <sup>29</sup> Tyndall MW, Craib KJ, Currie S, Li K, O'Shaughnessy MV, Schechter MT. Impact of HIV infection on mortality in a cohort of injection drug users. *J Acquir Immune Defic Syndr* 2001;**28**:351–57.
  - <sup>30</sup> Martin-Carbonero L, Benhamou Y, Puoti M *et al.* Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clin Infect Dis* 2004;**38**:128–33.
  - <sup>31</sup> Martinez-Sierra C, Arizcorreta A, Diaz F *et al.* Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfecting with hepatitis C virus and human immunodeficiency virus. *Clin Infect Dis* 2003;**36**: 491–98.
  - <sup>32</sup> Rosenthal E, Pialoux G, Rey D *et al.* Liver-related mortality in human immunodeficiency virus-infected patients in France (GERMIVIC cohort study, 1995–2003 In: *Proceedings of the 55th Annual Meeting of the American Association for the Study of Liver Diseases*. Boston, MA, 2001.
  - <sup>33</sup> Staples CT, Jr, Rimland D, Dudas D. Hepatitis C in the HIV (human immunodeficiency virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study (HAVACS): the effect of coinfection on survival. *Clin Infect Dis* 1999;**29**:150–54.