

Treatment, care and support for people co-infected with HIV and hepatitis C: a scoping review

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ABSTRACT

Background: Providing care for people who are co-infected with both HIV and hepatitis C virus (HCV) is becoming increasingly complex and requires integrated prevention, screening, support and programming efforts. We undertook a scoping review to provide a summary of the existing evidence base and to identify and assess the quality of treatment guidelines and systematic reviews related to 3 domains of interest: treatment; epidemiology; and care, support, programming and prevention.

Methods: We searched 7 databases, hand-searched 8 journals and contacted key informants to identify relevant literature. We included all primary research (including systematic reviews and meta-analyses) or treatment guidelines that assessed pegylated interferon and ribavirin for HCV or highly active antiretroviral therapy for HIV treatment, or both. In the epidemiology domain, we included all primary research (including systematic reviews and meta-analyses). Studies that included only people with hemophilia and those conducted in developing countries were excluded. In the care, support, programming and prevention domain, we included all studies and reports that focused on co-infection. Two reviewers independently applied coding criteria and assessed the quality of the treatment guidelines and systematic reviews using the Appraisal of Guidelines Research and Evaluation and A MeaSurement Tool to Assess Reviews instruments.

Results: Our search strategy yielded 1633 unique references. Of these, 227 references met the final inclusion criteria: 114 addressed treatment, 52 epidemiology and 79 care, support, programming or prevention. The references included 9 treatment guidelines: 4 were assessed as “strongly recommend,” 3 as “recommend (with provisos or alterations)” and 1 as “would not recommend” (1 could not be located). Of 10 systematic reviews that were located, 7 were assessed as being high quality, 2 as medium quality and 1 as low quality.

Conclusion: This quality-assessed inventory of treatment guidelines and systematic reviews can be used by physicians and service providers to rapidly locate research about HIV–HCV co-infection. However, many treatment guidelines and reviews often indicate that treatment of current injection drug users and/or people with mental health issues should proceed on a “case-by-case basis.” Therefore, much of the evidence (particularly in the treatment literature) is limited in its scope and applicability to important populations that are vulnerable to HIV or HCV infection or co-infection.

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THE AVAILABILITY AND ACCESSIBILITY OF HIGHLY active antiretroviral therapy (HAART) in Canada has extended the length and improved the quality of life of people with HIV.^{1,2} As a result, important co-morbidities are now emerging among people living with HIV. This has increased the complexity of their health and health care needs.³⁻⁵ The hepatitis C virus (HCV) commonly affects people with HIV and is a leading cause of death among people with HIV.^{1,6}

Currently in Canada, it is estimated that a large proportion (18%) of people with HIV are co-infected with HCV.⁷ The strongest predictor or risk factor of co-infection is a history of injection drug use (IDU), with co-infection rates estimated to range from 50% to 92%.⁷⁻²⁰ As a result, the populations affected most severely by co-infection are those in which IDU is most prevalent, such as current and former prisoners and Aboriginal people (First Nations, Inuit and Métis).¹⁶ For instance, 2 separate studies in Ontario and Quebec prisons found that the prevalence of HCV among inmates infected with HIV was 68% and 64.8%, respectively.^{21,22}

Combination HCV therapy with pegylated interferon and ribavirin is available for some people with HIV-HCV co-infection; however, the likelihood of treatment success (sustained virological response, defined as plasma free of HCV 6 months after completion of therapy) is diminished in people with HIV-HCV co-infection (genotype 1: ~15%–30%, genotype 2, 3: ~55%–60%)^{23,24} compared with people infected with HCV alone (genotype 1: ~40%–50%, genotype 2, 3: ~70%–90%).^{25,26}

Box 1: Scoping reviews

In general, the aim of a scoping review is to “map *rapidly* the key concepts underpinning a research area and the main sources and types of evidence available” [emphasis in original].³¹ Scoping reviews are often conducted for 4 reasons: “to examine the extent, range and nature of research activity,” “to determine the value of undertaking a full systematic review,” “to summarize and disseminate research findings” and “to identify research gaps in the existing literature.”³²

Although scoping reviews do not provide the depth of analysis found in a systematic review, they still provide valuable knowledge support to practitioners, policy-makers and researchers. A scoping review can act as an efficient resource for a busy clinician by providing a list of existing systematic reviews and treatment guidelines that have already been assessed for quality. Similarly, health care managers and policy-makers may find a listing of quality-assessed reviews and treatment guidelines helpful, and the identification of gaps in the literature will aid in commissioning new research. Researchers can also use a scoping review to determine what areas of inquiry have sufficient evidence to conduct a full systematic review.

The design and implementation of programs to deliver effective medical care for patients with HIV-HCV co-infection should take into account the differences in the psychosocial and medical status between some individuals.²⁷ Research has consistently identified substantially lower quality of life and cognitive function and a higher prevalence of mental illness among patients co-infected with HIV and HCV.²⁸ Current guidelines state that treatment for HCV infection can be started for patients co-infected with HIV who currently use illicit drugs or have mental illness.²⁹ However, active drug use and mental illness and their associated morbidities, such as homelessness and lack of social support, represent an important barrier to accessing treatment and to drug adherence. In addition, the presence of active depression before HCV treatment with interferon-based therapies is highly predictive of the development of clinically important depression during therapy, which is associated with significantly low virological response and low adherence rates.³⁰ The treatment of mental illness in co-infected individuals before the administration of HCV treatment represents a critical step in the successful care and support of co-infected patients.

In response to these complex treatment issues and the need to support care and community service providers who work with people who are co-infected, we undertook a scoping review (i.e., a rapid but rigorous assessment of the literature; see Box 1 for a description of scoping reviews) to provide a summary of the existing evidence base and an inventory of relevant systematic reviews and treatment guidelines that are currently available. Our specific objectives were to identify and assess the quality of systematic reviews and treatment guidelines about treatment, care, support, programming and prevention, as well as about the epidemiologic profile of HIV and HCV co-infection. We describe the sources and types of available evidence, identify areas where systematic reviews could be completed and highlight where additional primary research is needed.

Methods

Literature search. We used 3 strategies — database searches, journal hand-searching and key contacts — to identify published and unpublished literature. Our search strategies were designed to provide a balance between a rapid assessment of the literature and a comprehensive survey of the literature about HIV-HCV co-infection. First, we searched 7 databases (MEDLINE, PubMed, Cochrane Library, PsycINFO, AIDSearch,

contacted relevant researchers from 5 Canadian universities (McGill University, University of Alberta, University of British Columbia, McMaster University and the University of Toronto) and 4 organizations in Canada in the field of HIV and HCV (University Health Network, Centre for Addictions and Mental Health, Insite – Supervised Injection Site and Vancouver Coastal Health Authority) and asked them to identify any published and unpublished works that would be relevant to our review.

Article review and selection. We used an iterative and reflexive approach to develop and apply inclusion and coding criteria to the search results. First, from the electronic database search results, 2 pairs of independent reviewers (MGW and a research assistant; MD and a research assistant) reviewed the first 200 titles and abstracts retrieved and assigned each a code based on whether the publication addressed a question about HIV–HCV co-infection, whether it studied or discussed a Canadian population or an international population, the study design and the subject area addressed. We then met as a team and created additional codes for specific study populations and subject areas of interest. Next, 2 pairs of independent reviewers (MGW and a research assistant; MD and a research assistant) reviewed all of the titles and abstracts identified in our initial searches and excluded those not related to HIV–HCV co-infection.

We then collectively developed inclusion criteria for 3 domains (treatment; epidemiology; and care, support, programming and prevention) and 2 pairs of independent reviewers (MGW and a research assistant; MD and a research assistant) applied the inclusion criteria to all remaining titles and abstracts. In the treatment domain, we included all primary research (including systematic reviews and meta-analyses) and treatment guidelines that assessed pegylated interferon and ribavirin for HCV (current standard of care) or HAART for HIV treatment, or both. In the epidemiology domain, we included primary research (including systematic reviews and meta-analyses). For both the treatment and epidemiology domains, we excluded studies that included only people with hemophilia and those conducted in developing countries. Because of the lack of literature on care, support, programming and prevention, for this domain we included all studies and reports that focused on co-infection.

Next, we collectively refined the coding framework to include 24 characteristics across 4 categories – study design, study population, country or region of study and scope of study. Using the full text of each article, 2 of us (MGW and MD) independently assigned the new codes to each of the included references (Boxes 2–4). Disagreements were resolved through discussion until consensus was reached.

Last, 2 pairs of independent raters assessed the quality of each of the included systematic reviews and treatment guidelines (disagreements were resolved through discussion until consensus was reached). For systematic reviews, 2 independent raters (MGW and a research coordinator) applied the AMSTAR (A MeaSurement Tool to Assess Reviews) instrument, which has strong face and content validity and has been shown to be the strongest quality-assessment tool for systematic reviews.^{33,34} The AMSTAR instrument produces a quality score between 0 and 11, with ranges representing low (scores of 0–3), medium (4–7) and high (8–11) quality.³⁵ For treatment guidelines, 2 independent raters (MGW and AC) applied the AGREE (Appraisal of Guidelines Research and Evaluation) instrument, which is designed to be used by a wide range of professionals, demonstrates strong reliability and is the only internationally tested instrument.³⁶ AGREE consists of 23 items (4-point Likert scales) across 6 domains, which are used to produce 3 possible conclusions: “strongly recommend,” “recommend (with provisos or alterations)” or “would not recommend.”³⁷

Results

Our search strategy yielded 1633 articles (2598 before duplicate removal). Of these, 227 met the final inclusion criteria (Fig. 1). The full bibliography of included articles is available at <http://www.ohtn.on.ca/Pages/Knowledge-Exchange/HIV-HCV-Scoping-Review.aspx>. Agreement for the 2 sets of reviewers (calculated only at the inclusion-assessment stage; Fig. 1) was fair, with Kappa statistics of 0.377 and 0.249.

Of the 227 articles, 9 were treatment guidelines and 10 were systematic reviews (Table 1). Of the 9 treatment guidelines, 4 were “strongly recommended,”^{38–41} 3 were “recommended (with provisos or alterations),”^{29,42,43} and 1 was classified as “would not recommend”;⁴⁴ 1 guideline could not be assessed because it could not be located.⁴⁵ Of the 10 included systematic reviews, 3 addressed topics related to treatment,^{46–48} 3 focused on epidemiology,^{47,49,50} 4 focused on care or support^{49,51–53} and 4 focused on prevention^{51,52,54,55} (5 reviews addressed more than 1 domain). Through our quality assessments of the included systematic reviews we found 7 to be of high quality,^{46,48,51–55} with only 2 rated as medium quality^{49,50} and 1 as low quality.⁴⁷

We found 114 publications or reports in the treatment domain, 52 in the epidemiology domain and 79 in the care, support, programming and prevention domain (Boxes 2–4). Across all 3 domains, most of the studies were either local or national or involved multiple cities. Most of the treatment studies were from Europe (n = 64) and the United States (n = 33). In the

Box 2: Key findings: treatment for HIV–HCV co-infection**Types of literature available**

Total number of studies included = 114

Study design

Treatment guidelines: 10

Systematic reviews: 3

Randomized controlled trials: 17

Health technology assessment: 1

Longitudinal (prospective): 48

Longitudinal (retrospective): 13

Cross-sectional, case study or case-control: 19

Qualitative: 1

Grey literature studies: 2

Populations studied

Injection drug users: 5

Women: 3

MSM: 2

Aboriginal people: 1

Youth: 1

Other (clinic, hospital or institution based): 75

Other: 22

Country or regions studied

Western Europe: 64

United States: 33

Canada: 14

Australia: 7

Other: 6

Scope of studies

Local: 53

Multi-city or national: 46

Multi-country: 9

Key findings**Canada-specific findings**

- Canada has treatment guidelines for HIV and HCV co-infection (published in 2004 and updated in 2007)^{29,39} with the most recent being consistent with international guidelines.^{38,40-42,44,45}
- Canadian guidelines encourage clinicians to assess people with mental illness or injection drug users for HCV treatment on a case-by-case basis.^{29,39}

General findings

- The current standard for treating HCV is co-administration of pegylated interferon alpha and ribavirin, which takes 12–48 weeks depending on factors such as HCV genotype.²⁹
- Simultaneous initiation of treatment for both HIV and HCV is not advised owing to combined side effects.³⁹ The decision about which virus to treat first is based on the stage of HIV disease (as measured by CD4 count):²⁹
 - for individuals with CD4+ cell counts > 350 x 10⁹ cells/L and relatively low plasma HIV RNA levels and no history of alcohol abuse, HCV should be treated before initiating antiretroviral therapy for HIV;^{38-42,44,45}
 - for individuals with CD4+ cell counts < 200 x 10⁹ cells/L, HCV should be treated only after antiretroviral therapy has been initiated, plasma HIV RNA levels are suppressed, and CD4+ cell counts have risen;^{38-42,44,45}
 - for individuals with CD4+ cell counts between 200 x 10⁹ and 350 x 10⁹ cells/L and already on antiretroviral therapy for HIV, treatment for HCV may be considered after assessing factors such as the severity of liver disease, HCV genotype and the extent of suppression of HIV replication.^{38-42,44,45}
- HCV treatment is not recommended for individuals with current or previous liver decompensation and is contraindicated for pregnant women.³⁸⁻⁴⁵

Side effects

- People receiving treatment for HCV experience significant side effects, such as loss of appetite, nausea, anemia, depressive symptoms and mood changes⁵⁹ and need close monitoring.²⁹ Strategies to manage side effects include therapies such as erythropoietin for anemia and antidepressants⁵⁹ as well as individual or group counselling, harm-reduction and peer-support groups.⁶⁰

Treatment eligibility

- Co-infected individuals who have mental illness or are injection drug users have traditionally been excluded from clinical trials and treatment because of predicted poor adherence to or psychiatric side effects of HCV treatment or both; thus, little is known about the efficacy of HCV treatment in these populations.^{38-42,44,45,61}

HCV = hepatitis C virus, MSM = men who have sex with men.

Box 3: Key findings: epidemiology of HIV–HCV co-infection**Types of literature available**

Total number of studies included = 52

Study design

Systematic reviews: 3
 Randomized controlled trials: 1
 Longitudinal (prospective): 16
 Longitudinal (retrospective): 2
 Model: 3
 Policy or position paper: 2
 Cross-sectional, case study, case-control: 26
 Qualitative: 2
 Grey literature studies: 5

Populations studied

Injection drug users: 24
 Women: 2
 MSM: 2
 Aboriginal people: 4
 Youth: 6
 Mental health: 5
 Prisoners: 8
 Other (clinic, hospital or institution based): 14
 Other: 7

Country or regions studied

Western Europe: 13
 United States: 25
 Canada: 16
 Australia: 3
 Other: 4

Scope of studies

Local: 20
 Multi-city or national: 27
 Multi-country: 3

Key findings**Canada-specific findings**

- In 1999, about 11 194 people in Canada were estimated to be co-infected with HCV and HIV. Of those co-infected, 87% lived in 3 provinces: 34% in Quebec, 29% in British Columbia and 25% in Ontario.¹⁵
- Among those infected with HIV, the prevalence of co-infection is estimated to be 18%.¹⁵
- Injection drug users and men who have sex with men who use injection drugs made up 71% and 15%, respectively, of those co-infected in Canada in 1999; in British Columbia, 16% of youth injection drug users are estimated to be co-infected.^{11,15}
- The risk of co-infection is higher for Aboriginal people (First Nations, Inuit, Métis) and current and former injection drug users who are incarcerated than for other people.¹⁵ In 1999, about 1477 Aboriginal people and 611 people in federal and provincial prisons were co-infected.¹⁵
- Among inmates (based on a study with youth and adult inmates across 12 facilities in Ontario):²¹
 - The rates of HCV infection are significantly higher among adult women than among men;
 - The prevalence of co-infection was significantly higher among those with a self-reported history of injection drug use;
 - Of the 25 adults who were infected with HIV, 17 were HCV positive, giving a prevalence of 68.0%. Of the 282 adults who had HCV, 17 were HIV positive;
 - The current HIV prevalence rate among adult inmates (1.6%) is 9 x higher than the HIV prevalence estimated in the general population;
 - The current HCV prevalence rate among adult inmates (19.1%) is 24 x higher than in the general population (0.8%).

General findings

- Between 16% and 37% of people with HIV are co-infected with HCV.^{7,8,17,62}
- The strongest predictor or risk factor for co-infection is injection drug use; co-infection rates are estimated to be as high as 92% in some groups of injection drug users.⁷⁻¹⁷
- Rates of co-infection are also high in people who received transfusions of blood products and in men who have sex with men and who are also injection drug users.⁷
 - Co-infection rates are higher among prisoners who have HIV (11%–70%).⁶³
 - Individuals with serious mental illness are 8 times more likely than those in the general population to become infected with HIV and 11 times more likely to become infected with hepatitis C.⁶⁴

HCV = hepatitis C virus.

Box 4: Key findings: care, support, programming and prevention for HIV–HCV co-infection**Types of literature available**

Total number of studies included = 79
 Care, support and programming only: 43
 Prevention only: 5
 Care, support, programming and prevention: 31

Study design

Treatment guidelines: 1
 Systematic reviews: 6
 Randomized controlled trials: 3
 Longitudinal (prospective): 13
 Longitudinal (retrospective): 1
 Cross-sectional, case study, case-control: 19
 Qualitative: 8
 Grey literature studies: 11
 Model: 11
 Policy or position paper: 23
 Program evaluation: 5

Populations studied

Injection drug users: 49
 Women: 7
 Aboriginal people: 3
 Youth: 1
 Mental health: 11
 Prisoners: 17
 Other (clinic, hospital or institution based): 10
 Other: 7

Country or regions studied

Western Europe: 17
 United States: 36
 Canada: 21
 Australia: 6
 Other: 2

Scope of studies

Local: 22
 Multi-city or national: 47
 Multi-country: 5

HCV = hepatitis C virus.

Key findings**Canada-specific findings**

- There is presently no consensus or strategy direction at the provincial and federal levels as to whether HIV–HCV co-infection should be part of a broader HIV strategy or a broader HCV strategy. As such, funding streams for HIV and HCV have not been integrated, and coordinated interventions for co-infection are limited.^{6,65}
- This lack of strategic direction and coordination has resulted in a lack of available information and educational opportunities for physicians, health care providers and patients about HCV testing, treatment and care, and support required for the unique challenges faced in the context of co-infection.^{6,65}
- Despite Canada's treatment guidelines, many co-infected individuals who have a mental illness or are injection drug users, or both, are faced with various barriers to accessing HCV testing, treatment, care and support services. Many services that are available require abstinence from illicit drug use as a pre-condition to receive mental health and medical health services.¹³ Anticipated poor adherence, psychiatric side effects of HCV treatment and hesitation to take on patients who are injection drug users or who have mental illness are common barriers to accessing HCV treatment.¹³
- There are few HIV or HCV programs and services designed specifically for Aboriginal people, incarcerated women and incarcerated Aboriginal people.^{66,67}
- Although all national prisons fall under the same HIV/HCV policy direction as set by Correctional Services Canada, there is significant variability in pre- and post-test counselling, and barriers to optimal HIV combination therapy in most jurisdictions.^{66,67}

General findings

- Internationally, harm-reduction programs have a demonstrated ability to provide effective HIV and HCV prevention among vulnerable and high-risk populations including prisoners and injection drug users.^{66,67}

Canadian HIV/AIDS Policy & Law Review, and Google Scholar) from 1996 to January 2007 using combinations of search terms developed through consultation with a librarian at the University of Toronto (see for a full list of search terms). Given that our focus was on Canadian and North American content and that we wanted to perform a rapid assessment of the literature, we prioritized a relatively small subset of databases. Therefore, we selected MEDLINE and PubMed to capture treatment-related information, PsycINFO to capture literature related to mental health, AIDSearch to capture additional HIV-relevant literature, and Canadian HIV/AIDS Policy & Law Review to identify any policy-related documents that may not be indexed in the health sciences literature,

and Google Scholar to identify any additional grey literature. We then hand-searched 8 journals (*Canadian Medical Association Journal*, *AIDS Care*, *AIDS Policy and Law*, *Annals of Internal Medicine*, *Canadian Journal of Gastroenterology*, *HIV Medicine*, *Journal of Acquired Immune Deficiency Syndromes* and *New England Journal of Medicine*). These 8 journals were recommended by 2 members of our team (CLC and AC) who deal extensively with co-infection issues. For each journal, we reviewed all issues from January 2000 to January 2007 and identified all systematic reviews, treatment guidelines and primary research that addressed treatment, epidemiology, and/or care, support, programming and prevention for people co-infected with HIV and HCV. We also

Table 1: Systematic reviews and treatment guidelines: quality assessment and study characteristics

Reference	Domain	Study type	Quality*	Study characteristics		
				Time frame	Population	Interventions and topic
Sherman ²⁹	Treatment	Treatment guideline	Recommend (with provisos or alterations)	2007	Canada	Management of chronic HCV
Sherman ³⁹	Treatment	Treatment guideline	Strongly recommend	2004	Canada	Management of chronic HCV
Antonucci ⁴⁵	Treatment	Treatment guideline	Assessment was not completed†	2004	Italy	Management of HIV-HCV co-infection
Strader ⁴¹	Treatment	Treatment guideline	Strongly recommend	2004	United States	Diagnosis, management and treatment of HCV
Soriano ⁴⁰	Treatment	Treatment guideline	Strongly recommend	2004	Spain	Care for co-infected patients
CCD ³⁸	Treatment	Treatment guideline	Strongly recommend	2004	United States	Treatment of opportunistic infections in HIV-infected adults
Nelson ⁴⁴	Treatment	Treatment guideline	Would not recommend	2005	United Kingdom	Treatment for HIV and chronic HCV
Alberti ⁴²	Treatment	Treatment guideline	Recommend (with provisos or alterations)	2005	International	Treatment of chronic hepatitis B & C in HIV-infected patients
Boucher and Gruslin ⁴³	Treatment, care/support	Treatment guideline	Recommend (with provisos or alterations)	2000	Canada	Reproductive care for women living with HCV
Shepherd ⁴⁸	Treatment	Systematic review (part of an HTA)	High (8/11)	All literature up to 2003	HCV-infected patients from clinical trials	Pegylated interferon-2a and -2b with ribavirin
Kim ⁴⁶	Treatment	Systematic review	High (8/11)	All literature up to 2005	Co-infected patients in RCTs	Pegylated interferon and ribavirin
Mohsen ⁴⁷	Treatment, epidemiology	Systematic review	Low (2/11)	1993–2000	Outpatients, injection drug users, prisoners, MSM	Epidemiology and clinical implications of co-infection
Graham ⁵⁰	Epidemiology	Systematic review	Medium (4/11)	1966–1999	Co-infected patients with liver disease	Impact of HIV on the course of HCV
Gebo ⁴⁹	Epidemiology, care/support	Systematic review	Medium (6/11)	1996–2002	Patients with chronic HCV	Treatment and screening strategies for HCV
O'Connor ⁵³	Care/support	Systematic review	High (9/11)	All literature up to 2002	People facing health care decisions	Decision aids for treatment or screening decisions
Faggiano ⁵¹	Prevention, care/support	Systematic review	High (10/11)	All literature up to 2001	Injection drug users	Methadone maintenance programs
Leonard ⁵²	Prevention, care/support	Systematic review	High (8/11)	1997–1999	Injection drug users, prisoners and women	Needle exchange programs
Amato ⁵⁴	Prevention	Systematic review	High (9/11)	All literature up to 2004	Injection drug users	Tapered methadone doses
Gowing ⁵⁸	Prevention	Systematic review	High (8/11)	All literature up to 2003	Injection drug users	Oral substitution treatment for opioid dependence

HVC = hepatitis C virus, MSM = men who have sex with men, RCT = randomized controlled trial, HTA = health technology assessment.

* To assess the quality of treatment guidelines, we used the AGREE instrument, which consists of 23 items that are used to produce 3 possible conclusions: “strongly recommend,” “recommend (with provisos or alterations)” or “would not recommend.” To assess the quality of systematic reviews, we used the AMSTAR instrument, which produces a quality score between 0 and 11, with ranges indicating low (0-3), medium (4-7) and high (8-11) quality.

† We did not complete a quality assessment of Antonucci and colleagues because we were unable to locate a copy of the full paper.

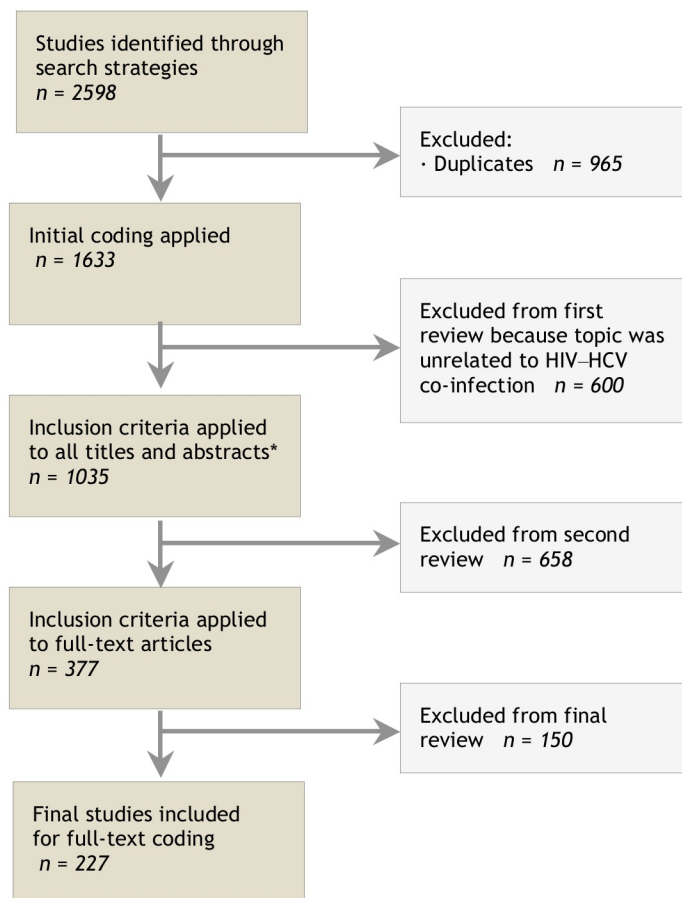


Figure 1: Study selection

* Kappa statistics were calculated only at this stage of reviewing because when the initial coding was applied studies were excluded only if they did not assess a topic related to HIV-HCV co-infection, and when the inclusion criteria were applied to the full-text articles, each review was reconciled through extensive discussion. Therefore, we determined that it was most appropriate to calculate agreement only when the inclusion criteria were first applied to all titles and abstracts.

treatment domain, we found 21 studies that included information related to both HAART for HIV and pegylated interferon and ribavirin treatment for HCV, 53 studies that investigated topics related only to HAART in co-infected people and 40 studies that investigated topics related only to pegylated interferon and ribavirin treatment in co-infected people. In the epidemiology domain, all of the 52 studies found included information related to epidemiologic trends of co-infection in key populations at high risk of HIV or HCV infection, or co-infection. Of these studies, 24 included current and former injection drug users, 8 included prison populations and 5 included people who had mental illness. In the care, support, programming and prevention domain, 43 studies addressed topics related to care, support and programming only, 5 addressed topics related to prevention only and 31 addressed both

topics. More than half of the publications and reports in this domain addressed issues related to IDU. (A full list of the references found for each of the 3 domains is available at <http://www.ohtn.on.ca/Pages/Knowledge-Exchange/HIV-HCV-Scoping-Review.aspx>.)

Discussion

Overall, we found that the literature on HIV-HCV co-infection is fairly well defined. We identified 9 treatment guidelines and 10 systematic reviews that addressed 1 or more of the 3 topic domains, which provides those delivering treatment, care and support with a reliable evidence base to draw from. The quality-assessed inventory of treatment guidelines and systematic reviews can be used by physicians and service providers to rapidly determine whether there are guidelines or reviews available that are specific to their jurisdiction and of sufficient quality to help with decision-making about treatment or other service-delivery issues.

Although we found a number of treatment guidelines and systematic reviews, many were based on literature that did not include current injection drug users or people with mental health issues because of limited evidence from these populations (especially in the treatment literature). As a result, guidelines and reviews often indicate that treatment in these populations should proceed on a “case-by-case basis.” This finding is particularly salient given that the epidemiologic literature indicates that co-infection is mostly found among current and former injection drug users.¹⁸ Therefore, much of the evidence (particularly in the treatment literature) either is limited in its scope and applicability to important populations that are vulnerable to HIV or HCV infection or co-infection, or lacks detail about how to deliver treatment to these populations while ensuring appropriate supportive care. Because active drug use and mental illness can reduce access to, adherence to and effectiveness of treatment for both HIV and HCV infections, programs to improve the health of co-infected patients must include a multidisciplinary approach using specialists in HCV and HIV treatment for injection drug users and those with mental illness.

The main clinical trials for HCV treatment involving HIV-HCV co-infected individuals used 800 mg per day of ribavirin.^{23,24} This is lower than the current standard

of care and may have diminished the sustained virological response obtained in these studies. In these studies, infected participants with genotype 2 or 3 received 48 weeks of therapy. It is not clear whether shorter treatment durations are equally effective. Additional evaluation of alternative dosing strategies in HIV–HCV co-infected populations is warranted. The HIV nucleosides used for HIV treatment in these early HCV studies (i.e., stavudine, didanosine, zidovudine) differ from those that are now used as part of standard practice. Each of these medications may have negative effects on overall tolerance of HCV therapy and sustained virological response. For example, combination didanosine–ribavirin therapy is now contraindicated because of increased risk of pancreatitis.^{23,56} The co-administration of zidovudine with ribavirin is not advised because it may exacerbate HCV treatment-related anemia and treatment-related fatigue, and increase the need for dose reduction, thereby diminishing sustained virological response.⁵⁷

In Canada, there are high levels of HIV–HCV co-infection among populations at high risk of HIV and HCV infection, such as current and former injection drug users, people with mental health illness and current and former prisoners. Thus, there is an increasing need to integrate prevention, screening, care, support and programming efforts and the funding streams for existing programs. An integrated programming and funding strategy will allow for populations to receive services for care, support and prevention, not only for HIV–HCV co-infection but also for other co-morbidities such as IDU and mental health issues.

The primary strengths of this scoping review are that it provides a rigorous systematic assessment of the literature on HIV–HCV co-infection across 3 domains, an inventory of treatment guidelines and systematic reviews that have been assessed for quality, a clear sense of the populations that have been a focus in the co-infection literature, and a direction for future research initiatives.

Several limitations of our scoping review should be highlighted. First, we did not include all relevant databases, such as EMBASE and CINAHL, which may have captured additional relevant publications that may not be found in MEDLINE. These databases were omitted because we wanted to conduct a relatively rapid review of the literature. We are confident that we captured much of the relevant literature available. Second, the agreement between reviewers was only fair (Kappa statistics 0.377 and 0.249). This low agreement is likely attributable to the fact that many abstracts were difficult to assess using our broad inclusion criteria, especially in the treatment domain since it was often difficult to discern the exact treatment regimen without

reviewing the full text. As a result, we were over-inclusive at the title- and abstract-review stage because we deemed it more important to ensure that we did not inadvertently exclude any relevant studies. Finally, because we wanted to focus on Canadian and other North American literature and to keep the review focused and rapid, we did not consider some important populations. Therefore, we excluded studies from developing countries and studies that focused only on people with hemophilia, deeming these to have different contexts that require separate analysis.

Our findings are not meant to be an exhaustive analysis of outcomes that would normally be found in a systematic review but rather are an outline of the primary themes that emerged from the systematic reviews, treatment guidelines, longitudinal studies and key references for care, support, programming and prevention that were included in this review. This outline of primary themes was prepared to provide a broad evidence base for the multi-stakeholder think tank that this scoping review was originally commissioned for.

Given the limited scope of some of the literature that we located, there is a need to expand co-infection research initiatives (particularly in the treatment and support domains) to injection drug users and mental health populations and to ensure that existing systematic reviews and treatment guidelines are updated as new data from these initiatives emerges. In addition, beyond the topics of methadone treatment and needle exchange for injection drug users, the literature about care, support, programming and prevention appears to lack enough depth for a full systematic review. Therefore, future research should attempt to evaluate or highlight integrated and interdisciplinary care models that use a harm-reduction approach for the treatment, care and support for people co-infected with HIV and HCV. Intervention research would help determine prevention efforts and support services for co-infected people and those at risk. Last, tracking the epidemiologic profile of HIV–HCV co-infection needs to continue with rigorous longitudinal models.

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Appendix 1: Database search terms

We used pre-specified search terms, including **HIV OR AIDS** combined with **Hepatitis C OR HCV**, which were then combined with a series of topic-specific text terms. The topic-specific terms were:

long-term survivors, HIV infections, health services, diagnostic services, community health services, quality of life, public health practice, comprehensive health care, primary health care, primary nursing care, managed care programs, delivery of health care (integrated), patient care management, patient care planning, clinical decision support systems, health planning support, mental health, socio-economic factors, health status, social environment, social class, determinants of health, health equity, patient care, clinical treatment.