Sex and gender differences in hepatitis C virus risk, prevention, and cascade of care in people who inject drugs: systematic review and meta-analysis

Anna Levinsson,[a,b,c] Camille Zolopa,[a,d] Farzaneh Vakili,[a,e] Sasha Udhesister,[a,e] Nadine Kronfli,[f,g] Mathieu Maheu-Giroux,[b] Julie Bruneau,[a,e] Heather Valerio,[h] Sahar Bajis,[h] Phillip Read,[i] Elisa Martró,[j,k] Lisa Boucher,[l] Leith Morris,[m] Jason Grebely,[h] Adelina Artenie,[n] Jack Stone,[n] Peter Vickerman,[n,o] and Sarah Larney[a,e,p,*]

[a]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada
[b]Department of Epidemiology and Biostatistics, School of Population and Global Health, McGill University, Montréal, Québec, Canada
[c]School of Public Health and Community Medicine, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden
[d]Department of Educational & Counselling Psychology, McGill University, Montréal, Québec, Canada
[e]Department of Family Medicine and Emergency Medicine, Université de Montréal, Montréal, Québec, Canada
[f]Division of Infectious Disease and Chronic Viral Illness Service, Department of Medicine, McGill University, Montréal, Québec, Canada
[g]Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montréal, Québec, Canada
[h]The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia
[i]Kirketon Road Centre, South Eastern Sydney Local Health District, Sydney, New South Wales, Australia
[j]Microbiology Department, Laboratori Clínic Metropolitana Nord, Hospital Universitari Germans Trias i Pujol, Institut d'Investigació Germans Trias i Pujol (IGTP), Badalona, Barcelona, Spain
[k]Biomedical Research Networking Center in Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[l]Department of Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[m]School of Public Health, Faculty of Medicine, Univerity of Queensland, Brisbane, Australia
[n]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom
[o]NIHR Health Protection Research Unit in Behavioural Science and Evaluation at University of Bristol, Bristol, United Kingdom
[p]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, Australia

eClinicalMedicine
2024;72: 102596
Published Online 10 April 2024
https://doi.org/10.1016/j.eclinm.2024.102596

Summary

Background People who inject drugs (PWID) are a priority population in HCV elimination programming. Overcoming sex and gender disparities in HCV risk, prevention, and the cascade of care is likely to be important to achieving this goal, but these have not yet been comprehensively reviewed.

Methods Systematic review and meta-analysis. We searched Pubmed, EMBASE and the Cochrane Database of Systematic Reviews 1 January 2012–22 January 2024 for studies of any design reporting sex or gender differences among PWID in at least one of: sharing of needles and/or syringes, incarceration history, injection while incarcerated, participation in opioid agonist treatment or needle and syringe programs, HCV testing, spontaneous HCV clearance, direct-acting antiviral (DAA) treatment initiation or completion, and sustained virological response (SVR). Assessment of study quality was based on selected aspects of study design. Additional data were requested from study authors. Data were extracted in duplicate and meta-analysed using random effects models. PROSPERO registration CRD42022342806.

Findings 9533 studies were identified and 92 studies were included. Compared to men, women were at greater risk for receptive needle and syringe sharing (past 6–12 months: risk ratio (RR) 1.12; 95% confidence interval (CI) 1.01–1.23; <6 months: RR 1.38; 95% CI 1.09–1.76), less likely to be incarcerated (lifetime RR 0.64; 95% CI 0.57–0.73) more likely to be tested for HCV infection (lifetime RR 1.07; 95% CI 1.01, 1.14), more likely to spontaneously clear infection (RR1.58; 95% CI 1.40–1.79), less likely to initiate DAA treatment (0.84; 95% CI 0.78–0.90), and more likely to attain SVR after completing DAA treatment (RR 1.02; 95% CI 1.01–1.04).

Interpretation There are important differences in HCV risk and cascade of care indicators among people who inject drugs that may impact the effectiveness of prevention and treatment programming. Developing and assessing the effectiveness of gender-specific and gender-responsive HCV interventions should be a priority in elimination programming.

*Corresponding author. Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada.
E-mail address: sarah.larney@umontreal.ca (S. Larney).

Funding Réseau SIDA-MI du Québec.

Keywords: Sex and gender differences; People who inject drugs; Hepatitis C virus

Research in context

Evidence before this study

We searched PubMed for systematic reviews relating to sex and gender differences in HCV risk, prevention, and cascade of care among people who inject drugs (("hepatitis C OR HCV") AND ("people who inject drugs" OR PWID) AND ("sex difference" or "gender difference" or "sex and gender difference")). There were reviews of sex and gender differences in HCV prevalence and incidence. A 2019 publication reported that globally, HCV antibody prevalence was lower among women who inject drugs than men who inject drugs (49% compared to 56%) but there was regional variation in this pattern. In a 2023 review, HCV incidence was higher in women who inject drugs than men who inject drugs (relative risk 1.2; 95% confidence interval 1.1–1.3). Given these recent findings, we did not assess prevalence or incidence indicators in the current review.

Added value of this study

With this review, we have identified that sex and gender are often poorly distinguished in the literature, and sex- or gender-specific results are often not reported, even for indicators where a sex or gender difference could reasonably be hypothesised to exist, or where a sex or gender difference may have significant impacts on the population-level outcomes of prevention or treatment programs. We have identified specific indicators and stages of the care cascade where there is evidence of a sex and/or gender difference, including risk behaviours and exposure to risk environments (with evidence that women are more likely to receptively share needles and syringes and men are more likely to be incarcerated); highly variable findings regarding opioid agonist treatment uptake and limited data regarding needle and syringe program use; HCV testing and treatment uptake (weak evidence that men are less likely to be tested, but also evidence that women are less likely to commence treatment); and spontaneous clearance (with women being more likely to clear infection without treatment). There was evidence of a small, but unlikely to be clinically relevant, advantage to women in terms of sustained virological response (SVR) following treatment. Half the studies were from three countries, and fewer than 10% were from low- or middle-income countries.

Implications of all the available evidence

These findings suggest a need for greater attention to be given to sex and gender in research and service provision for people who inject drugs, particularly in low- and middle-income countries, which were largely missing from included studies. Research priorities include work to clarify the extent to which the observed associations are linked to sex, gender, or a combination of both, and the effectiveness of gender-responsive interventions that may address some of these differences. Harm reduction and clinical HCV services can use these findings to improve the design and delivery of services to address the observed disparities, such as gender-responsive programming to increase HCV treatment uptake among women who inject drugs.

Introduction

An estimated 39% of people who inject drugs globally are living with chronic HCV infection,[1] and this population constitutes the majority of new HCV infections in many countries.[2] As such, there is a significant focus in research and clinical practice on people who inject drugs as a key population for HCV prevention and treatment interventions, particularly in the context of HCV elimination efforts.

Sex and gender differences (see Box 1) have been observed in relation to HCV among people who inject. Female sex is associated with greater likelihood of spontaneous clearance of HCV infection,[3] potentially a function of sex differences in immunological functioning and inflammatory responses.[3] Relative to men who inject drugs, HCV incidence is 20% higher in women who inject drugs,[4] although there is national and sub-national variation. HCV antibody prevalence is similar among men and women who inject drugs except in east and south-east Asia and north Africa and the Middle East.[5] Differences in HCV incidence and prevalence are likely influenced by a constellation of gender-linked factors including power dynamics in injecting partnerships, duration of injecting, access to harm reduction services, and requiring assistance to inject.[6–10]

Sex and gender differences may occur at any of a myriad of points in the HCV continuum, including risk of infection, access to and use of prevention services, and treatment uptake and outcomes. However, with the exceptions of spontaneous clearance and HCV prevalence and incidence, sex and gender differences in HCV prevention and care have not been well characterised. Failure to identify and explicitly account for these differences in HCV prevention and treatment programming may

Box 1.
Sex and gender in health
Sex and gender are related but distinct concepts. Sex refers to biological attributes such as chromosomes, hormones, gene expression, and anatomy, while gender refers to culturally and socially constructed roles, behaviours, expressions and identities.[13,14] Sex and gender are often categorised as binary (sex: female or male; gender: girl/woman or boy/man) but there is variation, particularly for gender, which may be better characterised as a continuum.[13] Gender may be considered in four dimensions: gender identity (how an individual self-identifies and expresses this identification), gender roles (social expectations associated with a given gender), gender relations (how individuals are treated by others based on perceived and/or expressed gender identity), and institutionalized gender (societal distribution of power, resources and opportunities based on gender).[15] Sex and gender are important determinants of health behaviours, manifestations of disease, and responses to treatments. Failing to address sex and gender differences in health may mean that interventions do not benefit all people or intensify disparities in health status and outcomes.

impede progress towards the goal of eliminating viral hepatitis as a public health problem by 2030.[11,12] We therefore aimed to estimate sex and gender differences in HCV risk, prevention, and the cascade of care in people who inject drugs.

Methods

Overview

We completed a systematic review and meta-analyses. Analysed indicators included risk of HCV exposure, engagement with key prevention interventions, and the cascade of care. The review protocol was registered in PROSPERO (CRD42022342806) and reporting is in line with the PRISMA statement.[16]

Definitions of sex and gender vary between countries, studies, and over time. As such, we anticipated that the terms sex and gender might have been used interchangeably in the literature, preventing a straightforward attribution of an association between an indicator of interest and either sex or gender. Thus, in this paper we have opted for using 'women' and 'men' throughout, by which we mean both sex or gender, and have reported results comparing these two groups only. The Discussion includes an expansion on the sex and gender constructs potentially underlying an identified difference.

Indicators selected for review

From the literature, we identified and defined three indicators for risk of exposure to HCV where sex and gender differences are likely to present: *sharing of needles and/or syringes* (prioritising receptive needle and syringe sharing if various measures of sharing were reported), *previous or current incarceration event* (because incarceration is associated with increased risk of HCV acquisition,[17] and prisons are a focus for HCV testing and treatment programs in many countries), and *injection while incarcerated* (among individuals reporting current or previous incarceration). To evaluate differences between the engagement of women and men with key prevention interventions,[18] we defined two indicators, *participation in opioid agonist treatment* (OAT) and *needle and syringe program (NSP) use*, defined as any engagement with either of these interventions.

For the HCV care cascade, we evaluated risk ratios at five different steps: *ever tested for HCV* (including antibody or RNA testing), *spontaneous clearance* (defined as being HCV antibody positive, but no detectable RNA, in the absence of treatment for HCV infection), *initiating direct-acting antiviral (DAA) treatment* (self-report or confirmed via clinical records, with the denominator being those with chronic infection), *completing DAA treatment* (self-report or confirmed by clinical records, with the denominator being the number who initiated treatment), and *attaining sustained virological response (SVR*, defined as aviremia following DAA treatment, assessed via a blood test after treatment completion, with the denominator being people who completed treatment (i.e. as-treated analysis).

Inclusion and exclusion criteria

Studies were included if they were published after January 1, 2012, and before the last database search (January 22, 2024). This start date was selected to limit studies to those using DAA therapies and to ensure that findings reflected contemporary trends. Further inclusion criteria were reporting data disaggregated by sex or gender, for at least one indicator of interest. While the main population of interest were people who inject drugs, if a study reported indicators of interest in populations of people who use drugs or receiving OAT, studies were included on the basis that HCV infection in these groups likely reflects previous injecting drug use. We excluded studies that reported data exclusively for women or men or were not in English.

Data sources and search strategy

The search strategy (Supplementary Materials) was executed in three databases: PubMed, Embase, and the Cochrane Database of Systematic Reviews. Identified studies were uploaded on and deduplicated by the Covidence platform. Abstract screening and full-text review were completed by a random pair of reviewers drawn from the reviewer pool consisting of five people (AL, SL, CZ, SU, FV). Any disagreements were resolved through inspection by a third reviewer, and group discussion if necessary.

We additionally searched for systematic reviews related to each indicator. Reference lists of these reviews were searched to identify additional studies. When a study had previously been included in a systematic

review of one of our indicators, but the published paper did not report sex- or gender-specific data, we reached out to the authors to request these data. Grey literature was not searched.

Data extraction

Data were extracted as numerators and denominators for women and men, alongside the recall period (e.g. lifetime; past 12 months) if relevant. If a study included a regression analysis of an indicator with sex or gender as a main variable of interest, the unadjusted effect estimate was extracted, and we reached out directly to the authors to collect numerators and denominators. Data from each study were extracted by two reviewers (randomized pairs of CZ, SU, FV) independently into preformatted extraction sheets, and the two extractions were then combined and checked for discrepancies by a third reviewer (AL) for meta-analysis.

Study quality assessment

Given the variety of included indicators and study designs, and that most indicators were exposures rather than outcomes, we elected to assess studies on three aspects of study design: recruitment settings or strategies (with community recruitment, respondent-driven sampling, or community recruitment plus any service-based recruitment being low risk of bias, service-based recruitment being high risk of bias, and unclear if insufficient information was provided to determine this); the participation rate (with ≥75% taken as low risk of bias, <75% being high risk of bias, and unclear if insufficient information was provided); and, for longitudinal studies, follow-up rate (categorised as for participation rate). Findings from the risk of bias assessment informed interpretation of the robustness of findings.

Statistical analysis

Extracted data were analysed using R version 4.2.1 packages *meta*[19] and *metafor*.[20] Random effects meta-analyses were carried out and results presented as forest plots with risk ratios and 95% confidence intervals. Where data were extracted relating to multiple recall periods (e.g. past month, past 12 months, lifetime), meta-analyses were stratified by recall period and no overall estimate was calculated. For indicators reported in several populations (e.g. people who inject drugs, people receiving OAT), each was analysed separately and an overall estimate was also calculated.

Role of the funding source

This study was funded by the *Réseau-SIDA MI du Québec*. The funding body had no role in the study design; collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication. Anna Levinsson and Sarah Larney had full access to the dataset and all authors collectively made the decision to submit for publication.

Results

The literature search identified 8993 after de-duplication (Fig. 1). We included a total of 92 studies for which sex- or gender-disaggregated data were published, or data were provided by authors (n = 7 studies) for at least one indicator of interest. Supplementary Table S1 lists all included studies and which indicators were extracted from each study.

Studies were conducted in 26 countries, with nine (10%) conducted in multiple countries. The largest number of studies were conducted in the United States (n = 20, 22%), Australia (n = 15, 16%), and Canada (n = 13, 14%). There were 38 cross-sectional surveys, 17 community- or prison-based longitudinal cohort studies, 16 clinical cohort studies, 13 administrative database studies, and 8 clinical trials. Just over half of studies (n = 52; 57%) recruited participants exclusively from services such as OAT programs and NSP. Participation rates were low or unclear in 57 (63%) studies. For 19 studies that used longitudinal data to report the indicators of interest (i.e. those reporting on treatment completion and SVR), follow-up rates were high for 16, reflecting that most of these studies were clinical trials. Three observational clinical cohort studies of these indicators had low follow-up rates.

HCV risk

Shared use of needles or syringes

There were 29 studies reporting 32 estimates of needle and syringe sharing for both women and men (Supplementary Figure S1). For studies reporting lifetime needle and syringe sharing, null findings were common, and the summary estimate suggested no evidence of a difference between men and women in this indicator (risk ratio [RR] 1.01, 95% confidence interval [CI] 0.89–1.15) (Table 1 and Fig. 2). For studies reporting needle and syringe sharing over shorter time frames, point estimates typically suggested higher prevalence among women than men. There was evidence of higher levels of sharing among women relative to men for recall periods of up to six months ago (RR 1.38, 95% CI 1.09–1.76), and past 6–12 months (RR 1.12, 95% CI 1.01–1.23).

Current or previous incarceration event

A total of 15 studies reported 16 estimates of incarceration (Supplementary Figure S2). There was evidence that women were less likely to have been incarcerated, with risk ratios 0.72 (incarceration in the past twelve months; 95% CI) and 0.64 (ever incarcerated; 95% CI 0.57–0.73) (Table 1 and Fig. 2).

Injection while incarcerated

Four studies reported proportions of women and men with a history of injection drug use who reported injecting drugs while incarcerated (Supplementary Figure S3). In the 'ever while incarcerated' studies (n = 2), the summary estimate clearly showed higher

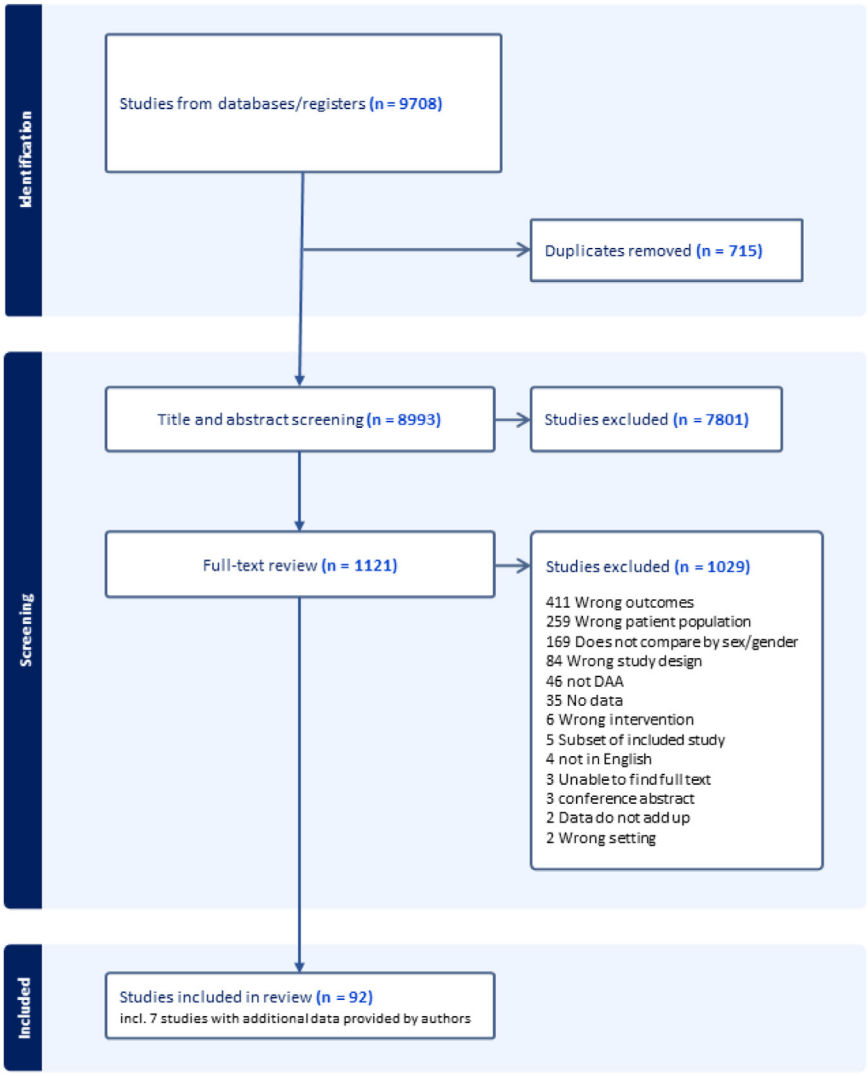

***Fig. 1:* PRISMA study inclusion flowchart**. PRISMA flowchart of retrieved and included studies. DAA: direct acting antiviral therapy.

injecting while incarcerated among men (RR 0.51, 95% CI 0.42–0.62). The summary estimate for 'during current incarceration' (n = 2) also suggested higher injecting while incarcerated among men, but with a wider confidence interval that included the null (RR 0.48, 95% CI 0.20–1.12) (Table 1 and Fig. 1).

HCV prevention

Participation in OAT

A total of nine studies presented sex- or gender-stratified data on lifetime OAT, including four studies of people who inject drugs, and five studies of people who use drugs. Findings were variable, but the overall estimate suggested greater lifetime engagement in OAT for women (RR 1.07, 95% CI 1.02–1.12) (Fig. 2 and Supplementary Figure S4). However, in those studies exclusively including people who inject drugs, the summary estimate was equivocal (RR 0.99, 95% CI 0.68–1.43) (Table 1 and Supplementary Figure S4). Among people who use drugs, there was evidence that women were 9% more likely to have ever received OAT (RR 1.09, 95% CI 1.05–1.12) (Table 1 and Supplementary Figure S4). When one very large study was removed from the analysis (Pro, 2020), the confidence interval was larger, but the summary effect size was unchanged (RR 1.09, 95% CI 0.99–1.20; forest plot not shown).

Use of needle and syringe programs

Only one study was identified with sex- or gender-stratified data on use of needle and syringe programs. Out of 11,897 individuals, 47% of men and 37% of women reported ever participating in an NSP (RR 0.79, 95% CI 0.72–0.86).

Indicator	Population	Recall period	N included studies	Risk ratio (95% CI), women compared to men	I^2
Needle and syringe sharing	PWID	Lifetime	12	1.01 (0.89, 1.15)	78%, $p < 0.01$
Needle and syringe sharing	PWID	Past 6–12 months	12	1.12 (1.01, 1.76)	63%, $p < 0.01$
Needle and syringe sharing	PWID	Past 6 months or less	8	1.38 (1.09, 1.76)	82%, $p < 0.01$
Incarceration	PWID	Lifetime	9	0.64 (0.57, 0.73)	96%, $p < 0.01$
Incarceration	PWID	Past 12 months	7	0.72 (0.59, 0.87)	74%, $p < 0.01$
Injecting while incarcerated	PWID	Lifetime	2	0.51 (0.42, 0.62)	0%, $p = 0.82$
Injecting while incarcerated	PWID	Current incarceration	2	0.48 (0.20, 1.12)	87%, $p < 0.01$
Receiving OAT	PWID	Lifetime	4	0.99 (0.68, 1.43)	97%, $p < 0.01$
Receiving OAT	PWUD	Lifetime	5	1.09 (1.05, 1.12)	92%, $p < 0.01$
HCV testing	PWID	Lifetime	13	1.06 (0.97, 1.15)	97%, $p < 0.01$
HCV testing	People on OAT	Lifetime	4	1.08 (1.03, 1.14)	63%, $p = 0.04$
HCV testing	PWUD	Lifetime	1	1.08 (1.01, 1.15)	N/A
Spontaneous clearance	PWID	N/A	4	1.61 (1.42, 1.83)	0%, $p = 0.70$
Spontaneous clearance	PWUD	N/A	1	1.08 (0.61, 1.89)	N/A
DAA initiation	PWID	Lifetime	11	0.85 (0.79, 0.91)	69%, $p < 0.01$
DAA initiation	People on OAT	Lifetime	3	0.75 (0.57, 0.99)	5%, $p = 0.35$
DAA completion	PWID	After initiating DAA treatment	7	1.01 (0.93, 1.11)	80%, $p < 0.01$
SVR	PWID	After completing DAA treatment	15	1.02 (1.01, 1.04)	0%, $p = 0.48$
SVR	PWUD	After completing DAA treatment	1	0.97 (0.73, 1.28)	N/A

Forest plots for each meta-analysis are provided in the Supplementary Materials. CI: confidence interval. PWID: people who inject drugs. OAT: opioid agonist treatment. HCV: hepatitis C virus. PWUD: people who use drugs. DAA: direct acting antivirals. SVR: sustained virologic response.

Table 1: **Findings of random effects meta-analyses of sex and gender differences in HCV indicators among people who inject drugs and related populations.**

HCV care cascade indicators

HCV testing

A total of 17 studies reported estimates of sex- or gender-stratified proportions of HCV antibody testing, of which 13 were among people who inject drugs and four were among individuals on OAT. The overall summary estimate suggested that HCV testing was 7% more common among women (RR 1.07, 95% CI 1.01–1.14) (Fig. 2 and Supplementary Figure S5). Among individuals on OAT, there was evidence that women were more likely than

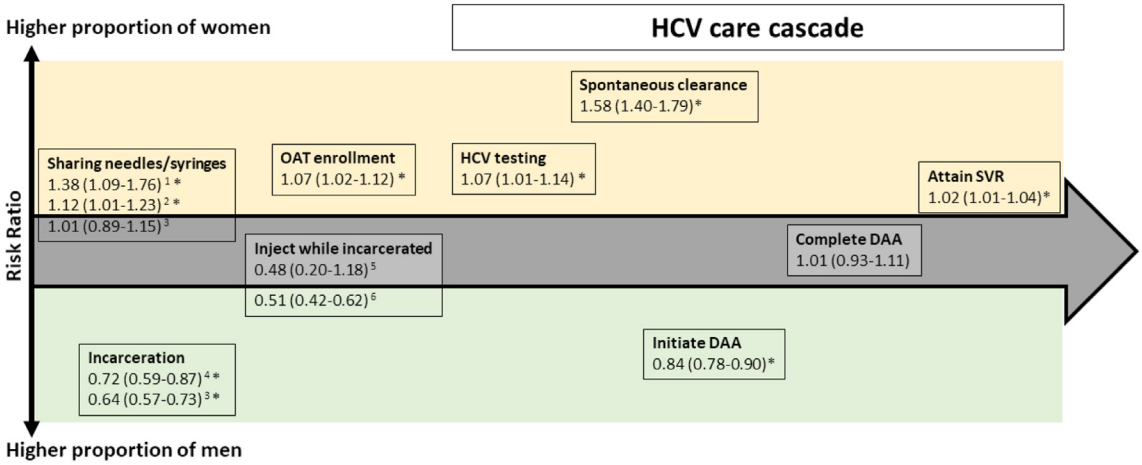

Fig. 2: **Schematic of overall findings by indicator**. Visual summary of findings. Indicators in the upper part of the figure are those where women were more likely to have the exposure. Indicators in the lower part of the figure are those where men were more likely to have the exposure. Indicators in the middle section are those where the confidence interval contained zero. From left to right, indicators move from HCV prevention and through the HCV cascade of care. OAT: opioid agonist treatment. HCV: hepatitis C virus. DAA: direct acting antiviral. SVR: sustained virologic reponse.

men to have ever been tested for HCV (RR 1.08, 95% CI 1.03–1.14) (Table 1). Among people who inject drugs, we found a similar point estimate, but a wide confidence interval, weakening the evidence of an association (RR 1.06, 95% CI 0.97, 1.15) (Table 1).

Spontaneous clearance

Five studies were included, four of people who inject drugs and one with people who use drugs. The overall summary risk ratio indicated a higher level of spontaneous clearance in women compared to men, with a summary RR of 1.58 (95% CI 1.40–1.79) (Fig. 2 and Supplementary Figure S6).

Initiation of direct-acting antiviral treatment

Fourteen studies reported sex- or gender-stratified data on the initiation of DAA treatment, eleven involving people who inject drugs and three, people on OAT. The overall summary estimate suggested that men were 16% more likely to initiate DAA treatment (RR 0.84 95% CI 0.78–0.90) (Fig. 2 and Supplementary Figure S7).

Completion of direct-acting antiviral treatment

There were seven studies reporting sex- or gender-stratified proportions of people who inject drugs completing DAA treatment. Aside from one study that found lower levels of DAA completion in women relative to men, all studies indicated no difference or higher levels in women (Supplementary Figure S8). The was no evidence of a difference between women and men in the proportion of people who inject drugs completing DAA treatment (RR 1.01, 95% CI 0.93–1.11).

Attaining SVR

Sixteen studies provided data on SVR following DAA treatment completion (fifteen in people who inject drugs, and one in people who use drugs). Study findings were clustered around the null. The summary estimate for people who inject drugs suggested an advantage to women in attaining SVR, but the magnitude of the effect is unlikely to be clinically relevant (RR 1.02, 95% CI 1.01–1.04) (Table 1, Supplementary Figure S9).

Summary of findings

Fig. 2 presents a summary of findings of overall meta-analyses (i.e. not stratified by sub-group). Where there was evidence that women experience a given indicator more often than men, the risk ratio is presented in the top half of the figure; risk ratios for indicators experienced more commonly by men than women are in the bottom half of the figure.

Discussion

Following a literature search identifying 90 studies reporting on ten HCV-related indicators, we provide evidence for sex and gender differences in HCV risk, prevention, and the cascade of care. Sex and gender were frequently poorly distinguished. More than half of the included studies (n = 48, 52%) were from the United States, Australia, or Canada, with only seven studies based in low- or lower middle-income countries, suggesting that there is a considerable geographic gap in data availability.

Random-effects meta-analyses demonstrated that among people who inject drugs, women were at greater risk for recent receptive needle and syringe sharing and have lower levels of HCV treatment uptake compared to men. In contrast, men were more likely to have been incarcerated, inject while incarcerated, and have lower likelihood of spontaneously clearing HCV infection. Importantly, a lack of detail in reporting of several prison-based studies (i.e. the denominator of how many individuals reported ever injecting drugs) prevented inclusion of several studies reporting on drug injecting while incarcerated. We did not find consistent evidence of a sex or gender difference in utilisation of OAT or HCV testing specific to the population of people who inject drugs. However, individual studies did show differences, suggesting that local contexts may be important influences over these indicators. A single study reported utilisation of NSP during the time frame that we examined; extending the search timeframe may have identified additional studies, but it is not clear if older studies would accurately represent current behaviours.

Whether an observed difference between women and men is due to sex, gender, or a combination of these will vary between indicators, and differences at different points in the HCV continuum may interact in complex ways. In terms of differences likely to be due to sex, spontaneous clearance may be due to sex-linked biological processes.[3] Other observed differences are more likely to be based in gendered roles, expectations, and relations. Research has documented women's vulnerability to receptive syringe sharing as a result of unequal power dynamics and gender-based violence in the context of romantic/sexual relationships with men who inject drugs,[6,21–23] but also that needle and syringe sharing can signify trust and intimacy in these relationships.[24,25] Efforts to address needle and syringe sharing must take these gendered dynamics into account.

Higher risk of incarceration among men who inject drugs may be linked to likelihood and seriousness of offending.[26] Given links between drug use, criminalisation, and HCV, custodial settings have become important settings for HCV testing and treatment.[27–29] High-volume testing and treatment in custodial settings has the potential to significantly reduce HCV prevalence and incidence among people who inject drugs, but may also, perversely, reinforce gender disparities in access to HCV care unless complementary efforts targeting women who inject drugs are enacted.[11]

One response to women's lower uptake of DAA treatment has been to recommend increased attention

to HCV testing and care in pre- and post-natal care.[30–33] Clinical guidelines from the American Association for the Study of Liver Diseases have been updated to recommend HCV testing of all pregnant persons at each pregnancy.[34] Australian data suggest that a majority of females of child-bearing age with HCV infection will give birth,[35] offering an opportunity to reach a large proportion of people with HCV, including those who may no longer use drugs or who are not in contact with harm reduction and/or drug treatment services. At the same time, we note that considerable efforts may be needed to overcome stigma and discrimination in pre- and post-natal care settings, and to address the concerns of pregnant people who inject drugs about the potential for negative consequences such as notification to child protection authorities in the event of a positive HCV test.[30] Furthermore, a greater focus on HCV care in pre- and post-natal settings should not preclude parallel efforts to enhance engagement of women and gender minorities who inject drugs in HCV treatment in harm reduction settings.

Due to conceptual confusion in the literature, and the lack of data relating to people with gender identities outside of cisgender men and women, it was not possible to specifically examine sex or the gender continuum as variables of interest. There is a need to better report how sex and/or gender are defined and measured, and to choose which of these is relevant for each specific use case. Guidance in this is available,[36] but enormous social and cultural variation in the extent to which sex and gender are differentiated and understood as separate concepts mean that researchers must take care in, or even avoid, applying standards that have been developed for contexts other than that where the research is being undertaken.

Data were derived from a multitude of study designs, including those usually considered less robust in the hierarchy of evidence. However, given the nature of the indicators under review, and our focus on ratios between men and women, the use of cross-sectional or single-group interventional studies should not necessarily lower confidence in the robustness of the findings. Studies frequently relied on recruitment via harm reduction services, which may bias sampling and indicators if there are systematic differences in the characteristics of men and women who inject drugs and attend services. We did not adjust analyses for other variables such as age or duration of injecting, which may differ between men and women who inject drugs. Most included studies were from high-income countries, precluding efforts to understand how sex and gender differences may vary between economic contexts. Heterogeneity was high in most meta-analyses, but with limited studies in each analysis it was difficult to undertake sub-analyses to explore sources of heterogeneity. High heterogeneity may also reflect underlying population differences among people who inject drugs in different cultural contexts. The search was completed in English only, but research suggests that including studies languages other than English in reviews has minimal impact on findings.[37] We restricted our search to 2012 onwards for all indicators; older data may exist in relation to OAT and NSP engagement, but these may not reflect contemporary realities. When sex- or gender-stratified estimates were not published, we contacted study authors in an effort to obtain additional data. This resulted in inclusion of some additional data, but there is considerably more data that have been collected but were not available for meta-analysis. Researchers are urged to consider publishing key outcomes and indicators stratified by sex and/or gender (as appropriate, depending on the outcome in question) as well as other key sociodemographic indicators that impact on health outcomes, such as racial or ethnic categorisations. It may not be statistically appropriate to interpret differences (or lack of differences) observed in individual studies if sample sizes are small; publication of stratified data will, however, facilitate future meta-analyses of differences according to these key determinants of health.

This review highlights that there are sex and gender differences in HCV risk, prevention, and the cascade of care. It is still unclear how these differences may interact over time within individuals and populations to influence progress towards HCV elimination. These findings suggest a need for gender-sensitive programming to avoid entrenching gender disparities in HCV treatment and cure and to facilitate elimination by 2030.

Contributors

AL contributed to study selection, reviewed all extracted data, completed the statistical analyses and prepared the figures, drafted the methods and results sections, and contributed to all other sections of the manuscript. CZ, FV, and SU completed study selection, risk of bias, and data extraction, and contributed to the manuscript. NK and MMG contributed to study design, obtained funding, and contributed to the manuscript. JB, AA, JS, and PV contributed to study design and manuscript writing. HV, SB, PR, EMC, LB, LM and JG provided additional data and contributed to the manuscript. SL completed the searches, contributed to study selection, drafted the introduction and discussion sections, and contributed to all other sections of the manuscript. All authors had full access to the study data and had final responsibility for the decision to submit for publication. AL and SL had direct access to and verified the underlying data reported in the manuscript.

Data sharing statement

Data collected for this study are available on request. Data are as extracted from published papers; unpublished data provided by study authors may only be shared with permission from the author who provided the data. A data sharing agreement outlining the data to be shared, the involvement of the original study investigators, and the agreed scope of work will be required.

Declaration of interests

AL, CZ, FV, SU, MMG, SB, LB, LM, JS report no conflicts of interest. AA reports funding from Wellcome Trust. NK reports research funding from Gilead Sciences, advisory fees from Gilead Sciences, ViiV Healthcare, Merck and Abbvie, and speaker fees from Gilead Sciences, Abbvie and Merck, all unrelated to this work. JB reports advisory board

fees from Gilead Sciences, Abbvie and Cepheid Sciences, all unrelated to this work. HV has received honorarium from Gilead Sciences, unrelated to this work. PR reports speaking and advisory board fees from Abbvie, Roche and Gilead Sciences, and research funding from Gilead Sciences unrelated to this work. EM reports lecture and consulting fees and research grants from Gilead Sciences unrelated to this work. JG reports being a consultant/advisor and having received research grants from AbbVie, Abbott, bioLytical, Cepheid, Gilead, Hologic, and Roche. PV reports unrestricted research funding from Gilead Sciences, unrelated to this work. SL reports advisory board fees from Gilead Sciences, unrelated to this work.

Acknowledgements

This work was supported by a grant from the Réseau SIDA-MI du Québec. SL and NK are supported by career awards from Fonds de Recherche du Québec - Santé. MMG's research program is supported by a Canada Research Chair (Tier 2) in Population Health Modeling. JB's research program is supported by the Canada Research Chair (Tier 1) in Addiction Medicine. PV is funded by the Health Protection Research Unit for Evaluation of Interventions and Behavioural Science [NIHR200877] funded by the UK National Institute for Health Research. PV, JS, AA and MMG are also funded by the Wellcome Trust (WT 220866/Z/20/Z). For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The Kirby Institute is funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government. JG is supported by a National Health and Medical Research Council Investigator Grant (1176131). FV is supported by a Bourse de Mérite de la Faculté de médecine de l'Université de Montréal. SU receives doctoral research support from the Canadian Network on Hepatitis C (CanHepC) Trainee Fellowship.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102596.

References

1 Degenhardt L, Webb P, Colledge-Frisby S, et al. Epidemiology of injecting drug use, prevalence of injecting-related harm, and exposure to behavioural and environmental risks among people who inject drugs: a systematic review. *Lancet Global Health*. 2023;11:e659–e672.
2 Trickey A, Fraser H, Lim AG, et al. The contribution of injecting drug use as a risk factor for Hepatitis C virus transmission globally, regionally, and at country level: a modelling study. *Lancet Gastroenterol Hepatol*. 2019;4:435–444.
3 Grebely J, Page K, Sacks-Davis R, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology*. 2014;59:109–120.
4 Artenie A, Stone J, Fraser H, Stewart D, Vickerman P. A global systematic review and meta-analysis of the incidence of HIV and hepatitis C virus (HCV) among people who inject drugs, and associations with age and sex or gender. *Lancet Gastroenterol Hepatol*. 2023;8:P533–P552.
5 Leung J, Peacock A, Colledge S, et al. A global meta-analysis of the prevalence of HIV, hepatitis C virus and hepatitis B virus among people who inject drugs - do gender-based differences vary by country-level indicators? *J Infect Dis*. 2019;220:78–90.
6 Irfan SD, Khan MNM, Khan SI. Tales of gender-based oppression and violence: risks and vulnerabilities of women who inject drugs (WWID) in Dhaka, Bangladesh. *Int J Drug Pol*. 2021;92:103144.
7 Värmå Falk M, Strömdahl S, Ekström AM, et al. A qualitative study of facilitators and barriers to participate in a needle exchange program for women who inject drugs. *Harm Reduct J*. 2020;17:1–10.
8 Sabri B, Greene MC, Du S, et al. Exploring multilevel determinants of co-occurring violence, HIV, mental health and substance use problems. *J Ethnic Cult Divers Soc Work*. 2021;0:1–13.
9 El-Bassel N, Strathdee SA. Women who use or inject drugs: an action agenda for women-specific, multilevel, and combination HIV prevention and research. *J Acquir Immune Defic Syndr*. 2015;69(Suppl 2):S182–S190.
10 Rosen JG, Glick JL, Zhang L, et al. Safety in solitude? Competing risks and drivers of solitary drug use among women who inject drugs and implications for overdose detection. *Addiction*. 2022;118:847. https://doi.org/10.1111/add.16103.
11 Larney S, Madden A, Marshall AD, Martin NK, Treloar C. A gender lens is needed in hepatitis C elimination research. *Int J Drug Pol*. 2022;103:103654.
12 WHO. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies; 2022. Accessed December 2, 2022.
13 Government of Canada CI of HR. How to integrate sex and gender into research - CIHR. https://cihr-irsc.gc.ca/e/50836.html; 2018. Accessed April 5, 2023.
14 LERU. *Gendered research and innovation: integrating sex and gender analysis into the research process*. League of European Universities; 2015.
15 Raparelli V, Norris CM, Bender U, et al. Identification and inclusion of gender factors in retrospective cohort studies: the GOING-FWD framework. *BMJ Glob Health*. 2021;6:e005413.
16 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
17 Stone J, Fraser H, Lim AG, et al. Incarceration history and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018;18:1397–1409.
18 Palmateer N, Hamill V, Bergenstrom A, et al. Interventions to prevent HIV and Hepatitis C among people who inject drugs: latest evidence of effectiveness from a systematic review (2011 to 2020). *Int J Drug Pol*. 2022;109:103872.
19 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22:153–160.
20 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Software*. 2010;36:1–48.
21 Stoicescu C, Cluver LD, Spreckelsen TF, Mahanani MM, Ameilia R. Intimate partner violence and receptive syringe sharing among women who inject drugs in Indonesia: a respondent-driven sampling study. *Int J Drug Pol*. 2019;63:1–11.
22 Staton M, Strickland JC, Tillson M, Leukefeld C, Webster JM, Oser CB. Partner relationships and injection sharing practices among rural appalachian women. *Wom Health Issues*. 2017;27:652–659.
23 Mburu G, Limmer M, Holland P. Role of boyfriends and intimate sexual partners in the initiation and maintenance of injecting drug use among women in coastal Kenya. *Addict Behav*. 2019;93:20–28.
24 Seear K, Gray R, Fraser S, Treloar C, Bryant J, Brener L. Rethinking safety and fidelity: the role of love and intimacy in hepatitis C transmission and prevention. *Health Sociol Rev*. 2012;21:272–286.
25 Katzman C, Tuchman E. The intersection of women'S sexual pleasure and injection drug use. *Subst Abuse*. 2019;40:201–206.
26 Degenhardt L, Trevena J, Larney S, et al. Engagement with the criminal justice system among opioid dependent people: retrospective cohort study. *Addiction*. 2013;108:2152–2165.
27 Stone J, Lim AG, Dore GJ, et al. Prison-based interventions are key to achieving HCV elimination among people who inject drugs in New South Wales, Australia: a modelling study. *Liver Int*. 2022;43:569. https://doi.org/10.1111/liv.15469.
28 Hajarizadeh B, Grebely J, Byrne M, et al. Evaluation of hepatitis C treatment-as-prevention within Australian prisons (SToP-C): a prospective cohort study. *Lancet Gastroenterol Hepatol*. 2021;6:533–546.
29 Godin A, Kronfli N, Cox J, Alary M, Maheu-Giroux M. The role of prison-based interventions for hepatitis C virus (HCV) microelimination among people who inject drugs in Montréal, Canada. *Int J Drug Pol*. 2021;88:102738.
30 Marshall AD, Martinello M, Zolopa C, Treloar C, Larney S. Universal hepatitis C virus screening and treatment as part of prenatal care. *Lancet Gastroenterol Hepatol*. 2023;8:295–297.

31 Epstein RL, Moloney C, Garfinkel J, et al. Enhancing linkage to hepatitis C virus treatment following pregnancy in women identified during perinatal care. *Hepatol Commun*. 2021;5:1543–1554.

32 Gross MS, Ruth AR, Rasmussen SA. Respect women, promote health and reduce stigma: ethical arguments for universal hepatitis C screening in pregnancy. *J Med Ethics*. 2020;46:674–677.

33 Jhaveri R, Broder T, Bhattacharya D, Peters MG, Kim AY, Jonas MM. Universal screening of pregnant women for hepatitis C: the time is now. *Clin Infect Dis*. 2018;67:1493–1497.

34 AASLD IDSA. *HCV guidance: recommendations for testing, managing, and treating hepatitis C*. American Association for the Study of Liver Disease and the Infectious Diseases Society of America; 2023. https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_December_19_2023.pdf. Accessed February 22, 2024.

35 Valerio H, Alavi M, Marshall AD, et al. Factors associated with hepatitis C treatment uptake among females of childbearing age in New South Wales, Australia: a population-based study. *Drug Alcohol Rev*. 2023. https://doi.org/10.1111/dar.13688.

36 Becker T, Chin M, Bates N. Measuring sex, gender identity, and sexual orientation. Washington D.C.: National Academies of Sciences. *Eng Med*. 2022;30:83.

37 Nussbaumer-Streit B, Klerings I, Dobrescu AI, et al. Excluding non-English publications from evidence-syntheses did not change conclusions: a meta-epidemiological study. *J Clin Epidemiol*. 2020;118:42–54.