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Research Paper

Public health interventions, priority populations, and the impact of COVID-19 disruptions on hepatitis C elimination among people who have injected drugs in Montreal (Canada): A modeling study

Charlotte Lanièce Delaunay[a,b], Marina B. Klein[a,b,c,d], Arnaud Godin[c], Joseph Cox[a,b,c], Nadine Kronfli[a,b,c], Bertrand Lebouché[b,c,e], Carla Doyle[a], Mathieu Maheu-Giroux[a,*]

[a] Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada
[b] Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada
[c] Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada
[d] CIHR Canadian HIV Trials Network, Vancouver, British Columbia, Canada
[e] Department of Family Medicine, McGill University, Montreal, Quebec, Canada

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ABSTRACT

Background: In Montreal (Canada), high hepatitis C virus (HCV) seroincidence (21 per 100 person-years in 2017) persists among people who have injected drugs (PWID) despite relatively high testing rates and coverage of needle and syringe programs (NSP) and opioid agonist therapy (OAT). We assessed the potential of interventions to achieve HCV elimination (80% incidence reduction and 65% reduction in HCV-related mortality between 2015 and 2030) in the context of COVID-19 disruptions among all PWID and PWID living with HIV.

Methods: Using a dynamic model of HCV-HIV co-transmission, we simulated increases in NSP (from 82% to 95%) and OAT (from 33% to 40%) coverage, HCV testing (every 6 months), or treatment rate (100 per 100 person-years) starting in 2022 among all PWID and PWID living with HIV. We also modeled treatment scale-up among active PWID only (i.e., people who report injecting in the past six months). We reduced intervention levels in 2020–2021 due to COVID-19-related disruptions. Outcomes included HCV incidence, prevalence, and mortality, and proportions of averted chronic HCV infections and deaths.

Results: COVID-19-related disruptions could have caused temporary rebounds in HCV transmission. Further increasing NSP/OAT or HCV testing had little impact on incidence. Scaling-up treatment among all PWID achieved incidence and mortality targets among all PWID and PWID living with HIV. Focusing treatment on active PWID could achieve elimination, yet fewer projected deaths were averted (36% versus 48%).

Conclusions: HCV treatment scale-up among all PWID will be required to eliminate HCV in high-incidence and prevalence settings. Achieving elimination by 2030 will entail concerted efforts to restore and enhance pre-pandemic levels of HCV prevention and care.

Introduction

If untreated, chronic hepatitis C virus (HCV) infection can cause cirrhosis, liver cancer, and death (Manns et al., 2017). Direct-acting antivirals (DAAs) cure HCV in over 95% of those treated, regardless of co-infection with HIV (Sulkowski et al., 2015). The *World Health Organization*'s (WHO) targets for HCV elimination as a public health threat include reductions of 80% in chronic HCV incidence and 65% in HCV-related mortality between 2015 and 2030 (World Health Organization, 2016).

In Canada, 85% of new HCV infections are diagnosed among people who have injected drugs (PWID) –a priority population for elimination (Jacka et al., 2020; Lanièce Delaunay, et al., 2021a). PWID living with HIV are less likely to spontaneously clear HCV and experience faster

Abbreviations: ART, Antiretroviral Treatment; CrI, Credible Intervals; DAA, Direct-Acting Antivirals; HCV, Hepatitis C Virus; NSP, Needle and Syringe Program; OAT, Opioid Agonist Therapy; PWID, People Who have Injected Drugs; PY, Person-Years.

* Corresponding author.
E-mail address: mathieu.maheu-giroux@mcgill.ca (M. Maheu-Giroux).

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liver disease progression (Greub et al., 2000). By the time they develop end-stage liver disease, most PWID have ceased injecting (Manns et al., 2017; Montain et al., 2016) and ex-PWID should be considered for preventing HCV-related deaths.

In Montreal (Quebec, Canada), 82% of active PWID (i.e., people who report injecting in the past six months) use needle and syringe programs (NSP) and 33% are on opioid agonist therapy (OAT) –close to the 40% recommended coverage (Canadian Network on Hepatitis C, 2019). They are tested for HCV every 14 months on average (annual testing is recommended) (American Association for the Study of Liver Diseases, 2021; Leclerc et al., 2021). DAAs are universally accessible in Quebec and, in 2017, 33% of active PWID seropositive for HCV and 39% of active PWID seropositive for HCV and HIV had ever been treated for HCV infection (Leclerc et al., 2021).

HCV seroincidence remains high among active PWID in Montreal (21 per 100 person-years [PY] in 2017), and seroprevalence is higher among active PWID living with HIV (86% in 2018) than among all active PWID (69%) (Leclerc et al., 2021). However, those living with HIV are mostly engaged in care, and thus more easily reached by interventions –in 2018, 83% of active PWID living with HIV were on antiretroviral treatment (ART) in Montreal (Leclerc et al., 2021).

Traditionally, HCV prevention for PWID has relied on harm reduction programs such as NSP and OAT (Platt et al., 2017). Following the introduction of DAAs, studies have suggested that HCV "treatment-as-prevention" can reduce HCV incidence and prevalence among PWID (Iversen et al., 2019; Montaner, 2011; Pitcher et al., 2019). Results are context-dependent, but regular testing, broad DAA access, and high-coverage harm reduction programs are likely essential to any HCV elimination response (Pitcher et al., 2019).

However, few studies have explored elimination strategies implemented among and for PWID living with HIV specifically. One modeling study conducted in Spain showed that increasing DAA uptake among PWID living with HIV was unlikely to achieve the WHO incidence reduction target due to ongoing HCV transmission from HIV-negative PWID (Skaathun et al., 2018). Further, the effects of focused interventions on active and/or ex-PWID on HCV-related mortality are unknown.

Finally, starting in 2020, the COVID-19 pandemic has disrupted HCV prevention and care services for PWID across Canada and exacerbated the pre-existing overdose crisis (Canadian Centre on Substance Use & Addiction, 2020; Public Health Agency of Canada, 2020; Institut National de Santé Publique du Québec, 2022). The impact of these disruptions could have compromised recent progress towards elimination.

Informed by robust data, dynamic models of disease transmission can simulate the course of an epidemic under different *"what if"* scenarios and estimate the direct and indirect effects of interventions (Jit & Brisson, 2011). Our overall objective was to assess the potential of various intervention scenarios to achieve HCV elimination among all PWID and PWID living with HIV by 2030 in Montreal. Multiple local initiatives aim to eliminate HCV and we can leverage population-based surveys to inform elimination efforts (McGill University Health Centre Research Institute, 2019; Klein et al., 2010; Leclerc et al., 2021). To strengthen this evidence-base we: 1) examined different elimination strategies for PWID subgroups (all PWID or PWID living with HIV; active and/or ex-PWID); 2) evaluated how likely these strategies are to achieve both incidence and mortality reduction targets; and 3) explored how COVID-19-related disruptions could affect elimination efforts.

Methods

Model structure

We used a dynamic, deterministic, sex-stratified compartmental model of HCV and HIV transmission via injection drug use among PWID. Key model parameters are presented in Table 1, and the model's full description can be found elsewhere (Lanièce Delaunay, et al., 2021). Briefly, PWID are modeled from their first drug injection until death. We explicitly model three causes of death: background mortality among all PWID, liver-related mortality among those chronically infected with HCV, and AIDS-related mortality among PWID living with HIV. The rate of recruitment into the model replicates the observed decline in the active PWID population size from 11,700 in 1996 (Remis et al., 1998) to 3910 in 2010 in Montreal (Leclerc et al., 2014). PWID population size estimates after 2010 for either the whole province or neighboring cities are highly heterogenous and uncertain. As such, we assumed a stable population size of PWID in Montreal after 2010 (Agence de la Santé Publique et des Services Sociaux de Montréal, 2013; Centre Intégré de Santé et de Services Sociaux de Laval, 2021; Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale Nationale, 2022; Jacka et al., 2020).

We modeled three concurrent dynamics: HCV transmission, HIV transmission, and injection behaviors (Fig. 1). Seven compartments represent HCV infection and the care cascade: 1) susceptible to HCV infection (HCV-seronegative; all PWID enter the model through this HCV compartment); 2) acute infection (primary infection); 3) susceptible to HCV re-infection (HCV-seropositive); 4) acute infection (re-infection); 5) undiagnosed chronic HCV infection; 6) diagnosed chronic HCV infection; 7) under treatment. Seven compartments describe HIV infection and care cascade: 1) susceptible to HIV infection (all PWID enter the model through this HIV compartment); 2–4) living with HIV, not on ART, stratified by CD4 cell counts (>350 cells/mm^3, 200–350 cells/mm^3, <200 cells/mm^3), and 5–7) living with HIV, on ART, stratified by CD4 cell counts. Injecting behavior dynamics are modeled through three compartments: 1) active PWID not on OAT; 2) active PWID on OAT; 3) ex-PWID (regardless of OAT status). We assumed disassortative mixing by sex (Smith, et al., 2018) and proportional mixing by HCV status. Mixing patterns are allowed to vary from proportional to fully assortative by HIV status, between people susceptible to HIV infection or living with HIV and undiagnosed on one hand, and people living with HIV and diagnosed on the other hand (Lanièce Delaunay, et al., 2021b).

For both viruses, we used time-varying forces of infection that depend on prevalence among injecting contacts (depending on mixing by sex, HIV status, and injecting behaviours), NSP and OAT coverage, and treatment status of injecting partners (Lanièce Delaunay, et al., 2021b). Although HIV can be sexually acquired and transmitted by PWID and their partner, the preeminent risk of HIV transmission among PWID is through multi-person use of contaminated syringes or needles (Baggaley et al., 2006)(Boily et al., 2009). Given the low HIV incidence among PWID in Montreal (Leclerc et al., 2021), the high ART coverage among PWID living with HIV (Leclerc et al., 2021), the small role of sexual HIV transmission to HCV dynamics among PWID, and the uncertainty in sexual mixing patterns in this population, we did not model sexual transmission of HIV.

We modeled the impact of HIV infection and linkage-to-care on HCV natural history and care: people living with HIV are less likely to spontaneously clear HCV (Smith et al., 2016); those not on ART have higher HCV-related mortality rates (Hayashi et al., 2014); and those on ART have facilitated access to HCV testing and treatment (Bartlett et al., 2019).

Model parametrization and calibration

To inform model parameters, we used data from *SurvUDI*, the HIV/HCV bio-behavioural surveillance network among active PWID in Quebec (Leclerc et al., 2021) and the *Canadian Co-infection Cohort*, a prospective study of HIV-HCV co-infected people (Klein et al., 2010). We retrieved complementary information from the literature –primarily from systematic reviews and meta-analyses (Table 1).

We used the Bayesian sampling importance resampling algorithm for model calibration (Rubin, 1987). First, we used Latin hypercube sampling to sample 70,000 parameter sets from our prior distributions

Table 1
Key model parameter descriptions, values, prior distributions, and sources.

Parameters	Median value	Units	Source
Demography			
Yearly reduction the recruitment rate of active PWID[a,b]		%	
≤2010	4.8		(Leclerc et al., 2014; Remis et al., 1998)
>2010	0		Assumption
Background mortality rate	1/46	per PY[a]	(Mathers et al., 2013)
HCV natural history			
Spontaneous HCV[a,b] clearance rate		%	(Smith et al., 2016)
Among HCV+/HIV-	25		
Among HCV+/HIV+	16		
Relative increased spontaneous HCV clearance among females	2.16	–	(Grebely et al., 2014)
Acute phase duration	0.5	year	(Westbrook & Dusheiko, 2014)
Liver-related mortality rate	1/57	per PY	(Trickey et al., 2019)
Increased liver-related mortality among PLHIV[a] not on ART[a]	2.3	–	(Hayashi et al., 2014)
HIV natural disease progression			
Progression rate from >350 CD4 cell count to 200–350 CD4 cell count	0.17	per PY	(Cori et al., 2015)
Progression rate from 200 to 350 CD4 cell count to <200 CD4 cell count	0.18	per PY	(Cori et al., 2015)
AIDS-related mortality rate	0.20	per PY	(Cori et al., 2015)
HCV transmission			
Baseline HCV transmission rate	0.60	per PY	Calibration
Reduced HCV transmission and acquisition among people on OAT[a]	0.5	–	(Platt et al., 2017)
HIV transmission			
Baseline HIV transmission rate	0.25	per PY	Calibration
Reduced HIV transmission and acquisition among people on OAT	0.7	–	(MacArthur et al., 2012)
Reduced HIV transmission from PLHIV on ART	65	%	Calibration
Injecting behaviours			
Degree of assortative mixing by sex	25	%	Calibration
Degree of assortative mixing by HIV status	50	%	Calibration
Degree of assortative mixing by OAT status	50	%	Calibration
Injection cessation rate	1/14	per PY	(Montain et al., 2016)
Interventions			
HCV testing rate		per PY	(Leclerc et al., 2021)
2003	1/1.5		
2015	1/1.2		
HCV treatment rate		per PY	(Lanièce Delaunay et al., 2022)
<2015	0.05		
≥2015	0.20		
Relative increased HCV treatment rate among PLHIV[a] on ART[a]	1.5	–	Calibration
HCV treatment effectiveness		%	(Hajarizadeh et al., 2018)Rodriguez-Torres et al., 2012;
<2015	56		Torriani et al., 2004); (*Canadian Coinfection Cohort, manuscript in preparation*)
Among HCV+/HIV-	30		
Among HCV+/HIV+	90		
≥2015			
HCV treatment duration		year	(Hull et al., 2016)
<2015	0.75		
≥2015	0.23		
HIV testing rate		per PY	(Leclerc et al., 2021)
2003	1/0.98		
2015	1/0.82		
HIV treatment rate (>350 CD4 cell count)		per PY	
<2014	0		(Richardson et al., 2014; Tseng et al., 2015)
≥2014	0.26		Calibration
HIV treatment rate (200–350 CD4 cell count)		per PY	(Richardson et al., 2014; Tseng et al., 2015)
<2007	0		Calibration
≥2007	0.26		
HIV treatment rate (<200 CD4 cell count)	0.26	per PY	Calibration
HIV treatment discontinuation rate	0.05	per PY	Calibration
NSP[a] coverage		%	(Leclerc et al., 2021)
2003	68		
2015	86		
Effectiveness of NSP for preventing HCV	20	%	(Platt et al., 2017)
Effectiveness of NSP for preventing HIV	34	%	(Aspinall et al., 2014)
OAT engagement rate	0.32	per PY	(Leclerc et al., 2021)
OAT cessation rate	0.54	per PY	(Bao et al., 2009)
COVID-19-related disruptions			
Reduction in HCV testing and treatment rates	50	%	Assumption
Reduction in coverage of NSP and OAT	15		Assumption

[a] ART: antiretroviral treatment; HCV: hepatitis C virus; OAT: opioid agonist therapy; NSP: needle and syringe programs; PLHIV: people living with HIV; PWID: people who inject drugs; PY: person-years.

[b] The recruitment parameter is estimated from the yearly reduction in the population of active people who inject drugs and the yearly number of deaths. The male to female population ratio is maintained constant across time.

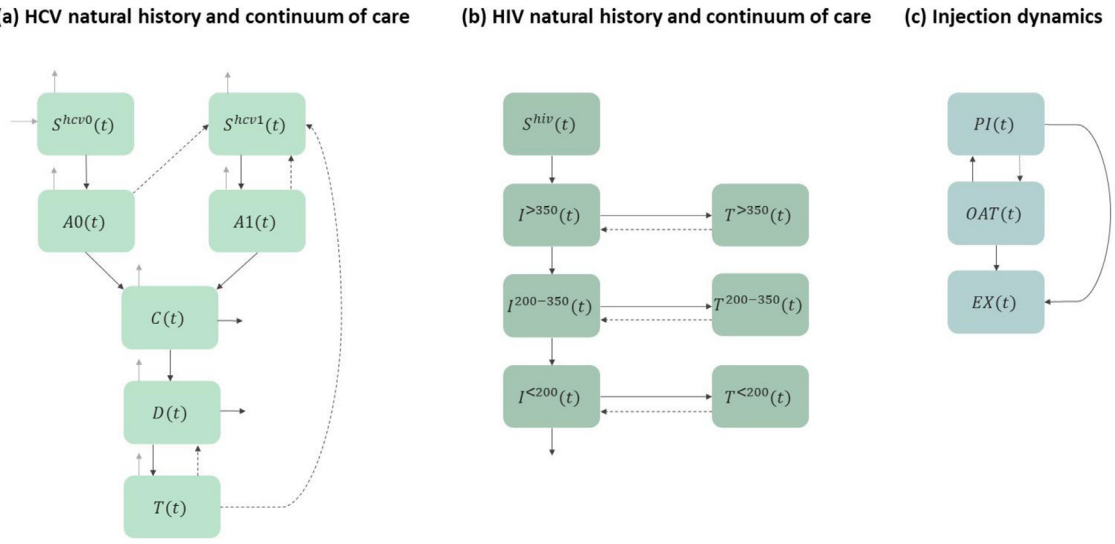

Fig. 1. (a) Hepatitis C virus (HCV) natural history and continuum of care. The model population is open, and people enter the model upon first injection (PI), as seronegative to HCV (S^{hcv0}) and HIV (S^{hiv}). They can become acutely infected with HCV at a time-dependent force of infection, and either spontaneously clear the virus or progress to chronic infection (C). If diagnosed (D), chronically infected people can initiate HCV treatment (T). In the absence of treatment, the disease progresses, and liver-related death can occur. When treatment is successful, people remain anti-HCV antibody-positive (S^{hcv1}) and can be reinfected. **(b) HIV natural history and continuum of care**. HIV susceptible people can acquire HIV at a time-dependent force of infection. Once infected, they progress through disease stages, represented by three decreasing CD4 cell count categories ($I^{>350}$, $I^{200-350}$, $I^{<200}$). AIDS-related death can occur when the CD4 cell count is inferior to 200 cells/mm^3. Antiretroviral therapy can be initiated among eligible individuals, and the model allows for treatment interruptions. **(c) Injection dynamics**. A fraction of people who inject drugs can initiate opioid agonist therapy (OAT). They are then assumed to inject at lower frequencies and are therefore less likely to acquire and transmit HCV and HIV. Opioid agonist therapy can also be interrupted. After an average duration of 14 years, people who inject drugs cease to inject permanently (EX). This figure was adapted from: Lanièce Delaunay C, Godin M, Kronfli N, Panagiotoglou D, Cox J, Alary M, Klein M, and Maheu-Giroux M, *Can hepatitis C elimination targets be sustained among people who inject drugs post-2030?, International Journal of Drug Policy*, Volume 96, 2021.

(McKay & Conover, 1979). For each parameter set, we ran the model to equilibrium using baseline parameter values. We used the population distribution across compartments at equilibrum to simulate epidemics from 2003 to 2018. In that period, we used the following annual estimates from *SurvUDI* as calibration targets: HCV seroprevalence, HCV seroincidence, HIV prevalence, HIV incidence, joint prevalence of anti-HCV antibodies and HIV, and ART coverage among those living with HIV. Based on these calibration targets, we estimated the likelihood of each sampled parameter set. From the initial 70,000 parameter sets, we resampled 350 sets with replacement using sampling weights proportional to their likelihood values. We used the resulting parameter sets for our simulations, thereby propagating parameter uncertainty to model outcomes.

As the last calibration data available were in 2018, we assumed constant parameter values from 2018 to March 2020. From March 2020 to May 2021, we modeled COVID-19-related disruptions by reducing access to HCV services. Based on emerging Canadian literature and information provided by local community organizations, we modeled a 50% reduction in HCV testing and treatment rates and a 15% reduction in NSP and OAT coverage (Canadian Centre on Substance Use & Addiction, 2020; Public Health Agency of Canada, 2020; Friesen et al., 2021; Van Gennip et al., 2021). We assumed that pre-COVID-19 intervention levels (i.e., 2018 parameter values) were restored in June 2021.

Intervention scenarios and model outcomes

Between 2022 and 2030, we simulated eight intervention scenarios, including a *status quo* scenario with unchanged intervention levels (Table 2). In other scenarios, intervention levels increased linearly to reach values provided in Table 2 in 2024, and then remained constant until 2030. We set a limit of 95% for HCV diagnosis and treatment coverage because existing interventions make it difficult to reach higher coverage. To isolate the impact of each intervention, we modeled them separately in the main analyses. We obtained intervention parameter values by triangulating information about current intervention levels in Montreal, Canadian public health guidelines, results from empirical and modeling studies, and consulting HCV care providers (Canadian Network on Hepatitis C, 2019; Cousien et al., 2017, 2018; Lanièce Delaunay et al., 2022; Leclerc et al., 2021). For each scenario, we generated point estimates using medians and 95% credible intervals (95%CrIs) for all outcomes described in Table 3.

Sensitivity analyses

We modeled scenarios combining previously described interventions. Due to uncertainty around the magnitude and duration of COVID-19-related disruptions in HCV services, we simulated the eight scenarios described above assuming no COVID-19 disruptions in 2020–2021. We also ran scenario 7 (increased treatment for all PWID; Table 2) with the following changes in COVID-19-related parameter values: 1) extending the same level of reduction in access to HCV services as initially modeled for an additional six months (i.e., 50% reduction in HCV testing and treatment rates; 15% reduction in coverage of NSP and OAT, March 2020-November 2021); 2) a smaller reduction in HCV services than initially modeled (40% reduction in testing and treatment rates; 10% reduction in harm reduction coverage); 3) a greater reduction in HCV services (60% reduction in testing and treatment rates; 20% reduction in harm reduction coverage); 4) a reduction in HIV services (50% reduction in HIV testing and treatment rates) in addition to reductions in HCV services and harm reduction.

Ethics

This study was approved by the *McGill University Health center Research Ethics Board* (REB#: MP-37-2019-4700). Our analyses were con-

Table 2
Public health intervention scenarios modeled from 2022 to 2030 among different subgroups of people who have injected drugs in Montreal (Quebec, Canada).

Scenario number	Intervention description	Priority population	Intervention parameter values			
			Opioid agonist therapy coverage	Needle and syringe program coverage	Baseline HCV testing rate	Baseline HCV treatment rate[a]
1	Status quo	–	33%	82%	85 per 100 PY	10 to 30 per 100 PY
2	Increased harm reduction coverage	Active PWID[b] living with HIV	40%	95%	85 per 100 PY	10 to 30 per 100 PY
3	Increased HCV testing rates	PWID living with HIV	33%	82%	200 per 100 PY	10 to 30 per 100 PY
4	Increased HCV treatment rates	PWID living with HIV	33%	82%	85 per 100 PY	100 per 100 PY
5	Increased harm reduction coverage	All active PWID	40%	95%	85 per 100 PY	10 to 30 per 100 PY
6	Increased HCV testing rates	All PWID	33%	82%	200 per 100 PY	10 to 30 per 100 PY
7	Increased HCV treatment rates	All PWID	33%	82%	85 per 100 PY	100 per 100 PY
8	Increased HCV treatment rates	All active PWID	33%	82%	85 per 100 PY	100 per 100 PY

[a] People living with HIV who are on antiretroviral treatment have higher HCV testing and treatment rates. The range of "*10 to 30 per 100 PY*" corresponds to the calibrated baseline treatment rate.
[b] People who report injecting drugs in the past six months.HCV: hepatitis C virus; PWID: people who have injected drugs; PY: person-years.

Table 3
Model outcome definitions, populations, and timeframes.

Outcome definition	Populations	Time frame[a]
Relative reduction in chronic HCV incidence	- All active PWID[b] - Active PWID living with HIV	2015–2030
Relative reduction in HCV-related mortality	- All PWID - PWID living with HIV	2015–2030
Relative reduction in chronic HCV prevalence	- All active PWID - Active PWID living HIV	2015–2030
Cumulative proportion of incident chronic infections averted as compared to status quo scenario	- All active PWID - Active PWID living HIV	2022–2030
Cumulative proportion of HCV-related deaths averted as compared to status quo scenario	- All PWID - PWID living with HIV	2022–2030
Ratio of number of HCV treatments initiated as compared to status quo scenario	- All PWID	2022–2030

[a] All intervention scenarios were modeled from 2022 to 2030. The *World Health Organization*'s targets for HCV incidence and mortality reductions are defined over the 2015–2030 timeframe.
[b] People who report injecting drugs in the past six months.HCV: hepatitis C virus; PWID: people who have injected drugs.

ducted using publicly available data sources. Hence, consent was not necessary for this study.

Results

Model calibration and pre-intervention period

Our calibrated model was able to reproduce all observed epidemiological outcomes (Additional file 1; Fig. 1) (Lanièce Delaunay, et al., 2021b). In 2015, year of reference for HCV elimination targets, the median modeled chronic HCV incidence was 12 per 100 PY (95%CrI: 10–15) among all active PWID, and 17 per 100 PY (95%CrI: 14–19) among those living with HIV. The median modeled HCV-related mortality rate was 5 per 1000 PY (95%CrI: 4–8) among PWID, and 9 per 1000 PY (95%CrI: 7–14) among PWID living with HIV. Fifty-one percent (95%CrI: 45–59) of all active PWID and 77% (95%CrI: 70–84) of those living with HIV were estimated to be chronically infected with HCV. Following universal coverage of DAAs in 2015, HCV incidence, prevalence, and mortality started decreasing (Fig. 2). In 2022, the modeled population size consisted of an estimated 5300 active PWID –14% living with HIV– and 18,000 ex-PWID.

Impact of COVID-19 disruptions

Between March 2020 and May 2021, reductions in access to HCV services could have led to small temporary increases in chronic HCV incidence (from 8.0 to 8.5 per 100 PY) and prevalence (from 30% to 31%).

Status quo

When keeping all intervention levels constant post-2022, the HCV incidence reduction target was met in 1% of simulations among all active PWID and 3% among those living with HIV. The posterior probabilities of achieving the mortality reduction target were 68% and 98% for PWID and PWID living with HIV, respectively. Between 2015 and 2030, chronic HCV prevalence decreased by a median of 58% (95%CrI: 47–69) among all active PWID and by 62% (95%CrI: 52–73) among those living with HIV. Nevertheless, 2080 (95%CrI: 1760–2330) PWID became chronically infected with HCV between 2022 and 2030, including 270 (95%CrI: 220–330) living with HIV. During the same period, 300 (95%CrI: 230–410) PWID died of HCV-related causes, of whom 50 (95%CrI: 40–70) were living with HIV.

Interventions among PWID living with HIV

Increasing harm reduction coverage (scenario 2) or HCV testing (scenario 3) among those living with HIV made little additional difference compared to status quo: incidence targets were not met more frequently among all active PWID or those living with HIV, and it was uncertain whether the mortality target could be achieved among all PWID (Fig. 2). Decline in chronic HCV prevalence was also similar to that modeled under the status quo. The increases in proportion of cumulative chronic HCV cases and HCV-related deaths averted (2022–2030) were negligible in comparison to status quo (Table 4). Scenarios 2 and 3 led to the same number of treatment initiations among all PWID between 2022 and 2030 as the status quo scenario (treatment initiation ratios of 0.99 (95%CrI: 0.99–1.00) and 1.00 (95%CrI: 1.00–1.00), respectively).

When increasing treatment among PWID living with HIV (scenario 4), the posterior probability of reaching incidence targets was 40% among all active PWID and 60% among those living with HIV (Fig. 2). Under this scenario, mortality targets were achieved in most simulations (94%) among all PWID and all of them among PWID living with HIV. Chronic HCV prevalence decreased by 73% (95%CrI: 65–80) between 2015 and 2030 among active PWID and by 91% (95%CrI: 88–93) among those living with HIV. Approximately one in four cumulative

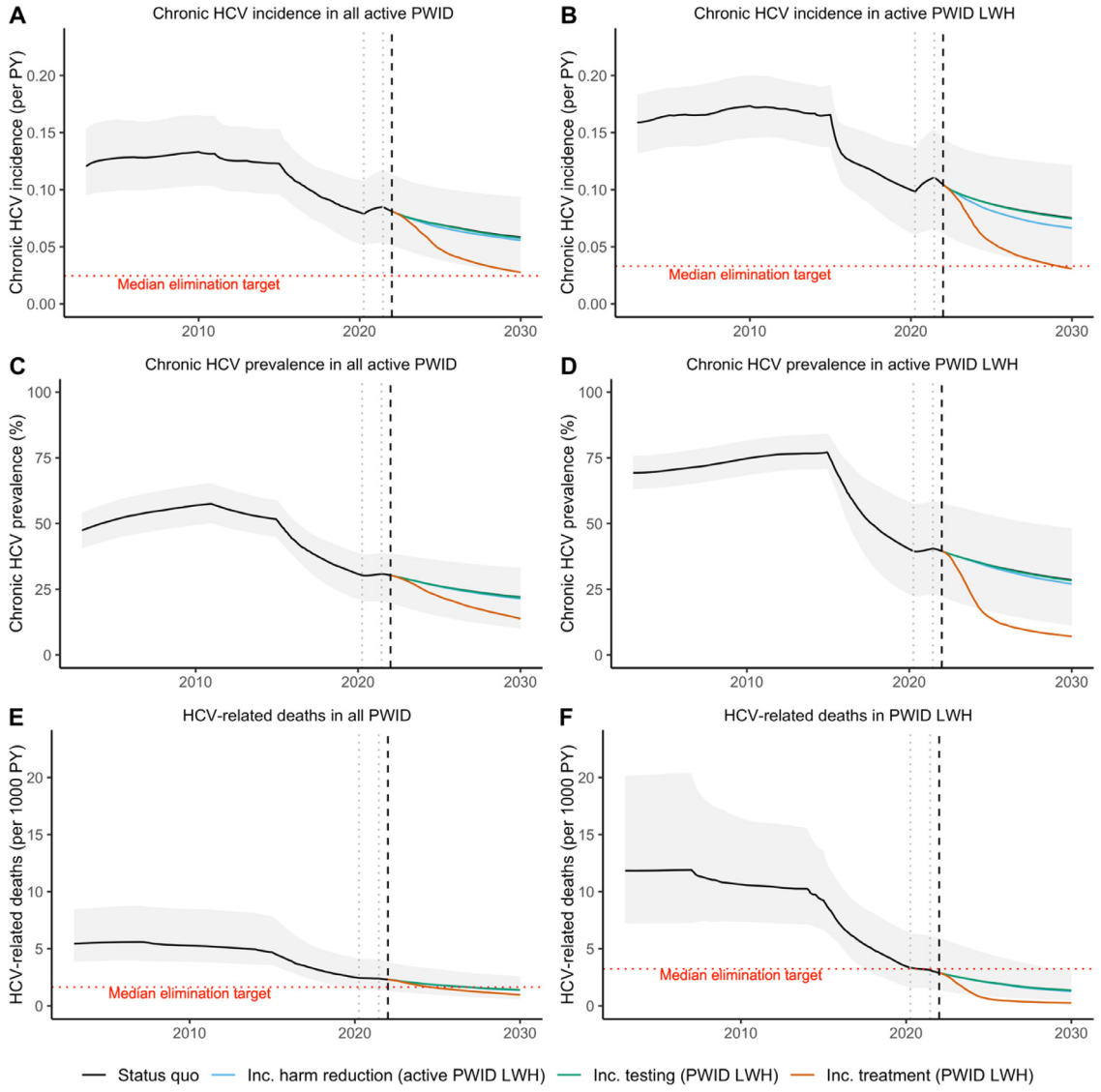

Fig. 2. Simulated chronic HCV incidence among all active PWID (i.e., people who report injecting in the past six months) (A) and active PWID living with HIV (B), chronic HCV prevalence among all active PWID (C) and active PWID living with HIV (D), and HCV-related mortality among all PWID (E) and PWID living with HIV (F) under various intervention scenarios implemented among PWID living with HIV in Montreal, Canada, from 2003 to 2030. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The grey dotted vertical lines represent the start (March 2020) and stop (May 2021) dates of modeled disruptions in HCV care and prevention services due to the COVID-19 pandemic. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. **Abbreviations**: HCV: hepatitis C virus; Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs.

chronic HCV infections was averted between 2022 and 2030 among all active PWID, and one in five among those living with HIV, as compared to the status quo (Table 4). One in six HCV-related deaths projected under status quo was prevented among all PWID, and over half among PWID living with HIV. Scenario 4 also led to 1.04 (95%CrI: 0.97–1.19) times more HCV treatment initiations among all PWID between 2022 and 2030, as compared to status quo.

Interventions among all PWID

Extending enhanced harm reduction (scenario 5) or testing (scenario 6) to all did not substantially impact chronic HCV incidence, prevalence, or mortality (Fig. 3). Yet, compared to status quo, increasing NSP and OAT coverage prevented 12% of cumulative chronic infections between 2022 and 2030 among all active PWID and 11% among those living with HIV (Table 4). Higher harm reduction coverage also prevented 3% of cumulative HCV-related deaths among PWID and 4% among PWID living with HIV. Scenario 5 led to 0.98 (95%CrI: 0.96–0.99) times less HCV treatment initiations among all PWID between 2022 and 2030. In scenario 6, the ratio of treatment initiations was 1.04 (95%CrI: 1.03–1.04) as compared to the status quo.

When increasing treatment for all PWID (scenario 7), HCV incidence and mortality reduction targets were met in all simulations, for both PWID and PWID living with HIV (Fig. 3). Between 2015 and 2030, chronic HCV prevalence was reduced by 95% (95%CrI: 94–96) among active PWID and by 96% (95%CrI: 95–97) among those living with HIV. This scenario also prevented a median of 44% cumulative incident chronic infections between 2022 and 2030 among PWID and 40% of these among PWID living with HIV (Table 4). Over half of HCV-related deaths projected to occur under status quo were prevented: 58% among PWID and 60% among PWID living with HIV. Finally, scenario 7 led to 1.39 (95%CrI: 1.14–1.92) times more HCV treatment initiations among all PWID between 2022 and 2030.

Table 4
Hepatitis C infections and deaths under various intervention scenarios among people who have injected drugs from 2022 to 2030 in Montreal (Quebec, Canada).

Scenario number	Intervention description	Priority population	Median proportion of cumulative chronic HCV infections averted from 2022 to 2030 (95%CrI)		Median proportion of cumulative HCV-related deaths averted from 2022 to 2030 (95%CrI)	
			Among active PWID living with HIV	Among all active PWID	Among PWID living with HIV	Among all PWID
1	Status quo	–	Referent	Referent	Referent	Referent
2	Increased harm reduction coverage[a]	Active PWID[b] living with HIV	7% (2–13)	3% (1–6)	2% (0–4)	1% (0–2)
3	Increased HCV testing rates	PWID living with HIV	0% (0–1)	0% (0–1)	0% (0–1)	0% (0–0)
4	Increased HCV treatment rates	PWID living with HIV	19% (0–41)	24% (8–38)	55% (42–65)	15% (9–20)
5	Increased harm reduction coverage[a]	All active PWID	11% (6–17)	12% (7–18)	4% (1–7)	3% (2–5)
6	Increased HCV testing rates	All PWID	1% (0–4)	1% (0–4)	1% (0–3)	2% (1–5)
7	Increased HCV treatment rates	All PWID	40% (32–48)	44% (38–50)	60% (50–68)	58% (49–64)
8	Increased HCV treatment rates	All active PWID	40% (32–48)	44% (38–50)	39% (28–46)	36% (31–40)

[a] Joint increase in the coverage of (1) needle and syringe programs, and (2) opioid agonist therapy.
[b] People who report injecting drugs in the past six months.CrI: credible interval; HCV: hepatitis C virus; PWID: people who have injected drugs.

Increased treatment among active PWID

With regards to HCV incidence and prevalence, increasing treatment among active PWID only (scenario 8) yielded the same results as scenario 7 (scaled-up treatment for all PWID). This intervention achieved HCV elimination targets for both PWID and PWID living with HIV. Yet, smaller fractions of HCV-related deaths were prevented between 2022 and 2030: 36% among PWID and 39% among PWID living with HIV. Scenario 8 also led to 1.19 (95%CrI: 1.06–1.47) times more HCV treatment initiations among all PWID between 2022 and 2030.

Sensitivity analyses

Jointly modeling interventions did not affect our results: sizeable effects were consistently driven by increased treatment: increases in testing or harm reduction coverage had little impact (Additional file 1; Figs. 2 and 3). Assuming no disruption in HCV services during the COVID-19 pandemic did not affect the qualitative ranking of scenarios (Additional file 1; Figs. 4 and 5). Similarly, varying the magnitude and duration of COVID-19-related reductions in HCV services or reducing access to HIV testing and treatment did not affect the outcomes of our scenario increasing HCV treatment among all PWID (Additional file 1; Fig. 6).

Discussion

Principal findings

DAA scale-up to levels beyond those reached in 2020 among all PWID diagnosed with HCV, irrespective of HIV status or time since last injection, was key to reaching HCV elimination targets by 2030 in Montreal. Focusing treatment efforts on PWID living with HIV –who can be reached by interventions and have high HCV acquisition and transmission risks– prevented many HCV-related deaths, especially among those living with HIV. This strategy led to substantial progress towards elimination but was insufficient to achieve it. Ex-PWID no longer contribute to onward HCV transmission via injection drug use. Yet, including them in treatment efforts is important to prevent HCV-related deaths. HCV transmission is high in Montreal and modeling COVID-19-related reductions in access to HCV services led to a modest, yet rapid epidemic resurgence among PWID. In addition to scaling-up treatment, it is essential that pre-COVID-19 levels of HCV testing and harm reduction are rapidly restored to ensure elimination by 2030.

Contextualization of results

Harm reduction coverage and HCV testing rates are already relatively high in Montreal. It is therefore not surprising that further increases in coverage had little impact. This is especially true for HCV-related deaths since our study period (2022–2030) is too short to observe the prevention benefits of harm reduction on HCV mortality. Previous modeling studies have also concluded that harm reduction strategies alone were unlikely to eliminate HCV among PWID (Pitcher et al., 2019). Nevertheless, NSP and OAT are cost-effective, prevent multiple drug-related harms, and may be instrumental to sustaining HCV elimination targets post-2030 among PWID (Lanièce Delaunay, et al., 2021b; Wilson et al., 2015). Harm reduction should remain at the core of elimination strategies for PWID. Bottlenecks can occur at different stages of the HCV care cascade. In settings where few PWID are aware of their HCV infection, increasing testing can reduce HCV prevalence (Blake & Smith, 2021). In settings like Montreal, where most PWID know their HCV status, further reducing time from infection to diagnosis may have little impact on HCV incidence or mortality (Cousien et al., 2018). These differences advocate for tailoring HCV elimination strategies to local challenges.

Evidence from modeling studies suggests that HCV treatment rates below 10 per 100 PY could achieve elimination among PWID in several settings (Pitcher et al., 2019). In Montreal, however, HCV seroincidence and seroprevalence remain high despite relatively high engagement in HCV prevention and care: higher treatment uptake would be necessary to reduce transmission. A modeling study suggests that HCV treatment rates of 200 per 100 PY could be cost-effective among PWID in France, where baseline chronic HCV incidence levels were comparable to those estimated with our model for Montreal (Cousien et al., 2018). Nevertheless, HCV treatment cost may vary widely across countries, and these results may not be generalizable to Canadian settings. In real-world programs like Iceland, treatment rates above 150 per 100 PY have been attained among PWID (Olafsson et al., 2019). We used a treatment rate of 100 per 100 PY as it was deemed achievable in our setting based on existing literature. Nevertheless, extensive public health efforts will

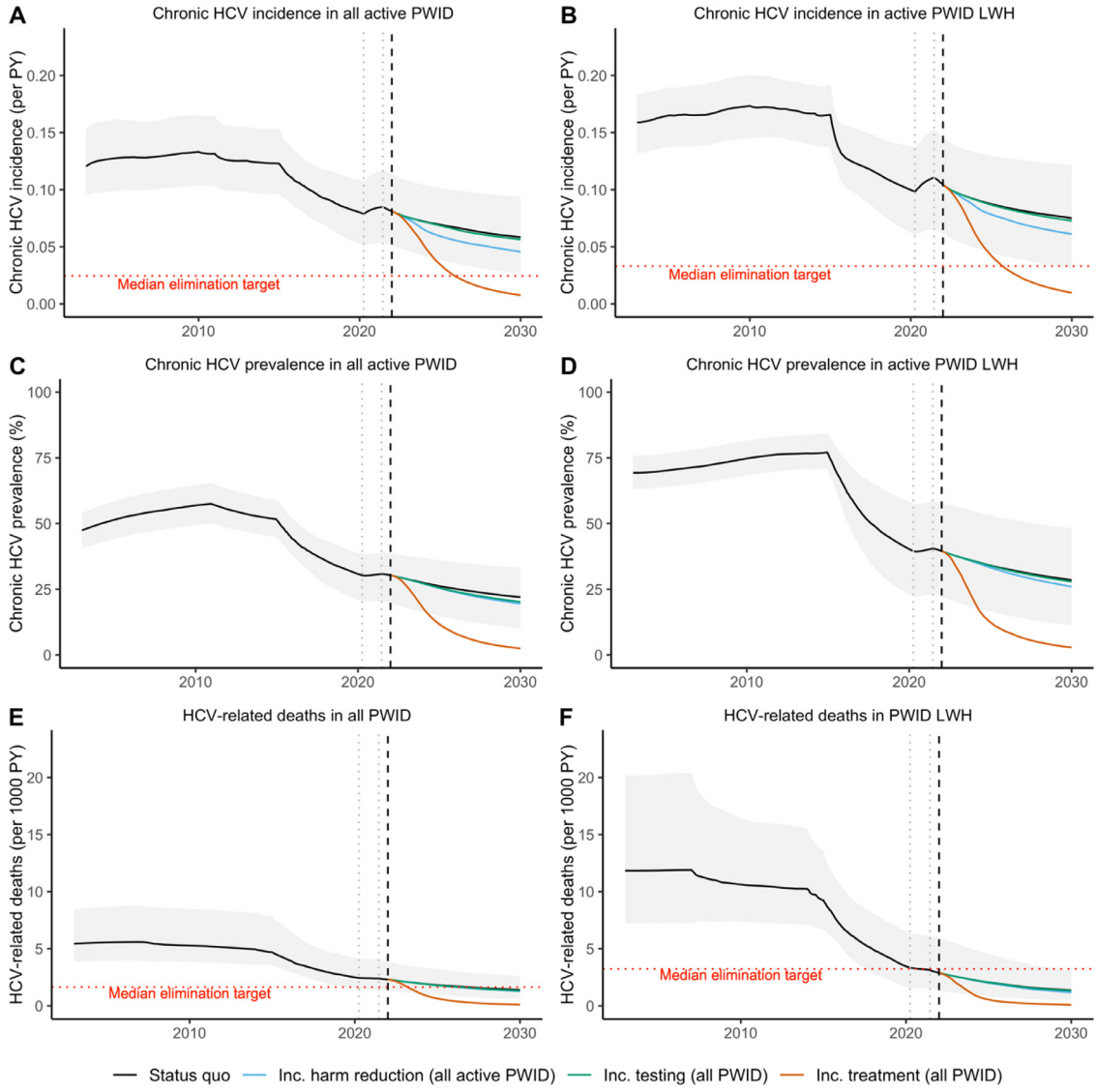

Fig. 3. Simulated chronic HCV incidence among all active PWID (i.e., people who report injecting in the past six months) (A) and active PWID living with HIV (B), chronic HCV prevalence among all active PWID (C) and active PWID living with HIV (D), and HCV-related mortality among all PWID (E) and PWID living with HIV (F) under various intervention scenarios implemented among all PWID in Montreal, Canada, from 2003 to 2030. The grey ribbons represent 95% credible intervals around estimates for the status quo scenario. The grey dotted vertical lines represent the start (March 2020) and stop (May 2021) dates of modeled disruptions in HCV care and prevention services due to the COVID-19 pandemic. The black dashed vertical line represents the start date (January 2022) of modeled intervention scenarios. **Abbreviations**: HCV: hepatitis C virus; Inc.: increased; LWH: living with HIV; PWID: people who have injected drugs.

be required to massively engage PWID in DAA treatment given current rates are approximately 10–30 per 100 PY. Local empirical data are warranted to determine how to reach and sustain this level of treatment.

Few studies have examined interventions to eliminate HCV among PWID while incorporating HIV transmission dynamics (Martin et al., 2018; Skaathun et al., 2018). Our results suggest that while not sufficient to meet the WHO incidence reduction target among all PWID, increasing HCV treatment among PWID living with HIV could lead to substantial progress toward this goal. Because our model tracks PWID who have ceased to inject, we could additionally show that focusing treatment efforts on PWID living with HIV could achieve the WHO mortality reduction target for all PWID.

Potential implications

Scaling-up DAA uptake among PWID is necessary to eliminate HCV in this population, and this could be achieved by macro-level policies such as funding health services, care models offering alternatives to hospital-based specialized HCV care, interventions facilitating health service utilization by patients and providers, and HCV education (Ortiz-Paredes et al., 2022). HCV treatment-as-prevention has generated optimism that we can reach and sustain HCV elimination as a public health threat among PWID (Lanièce Delaunay, et al., 2021b). Yet, the COVID-19 pandemic could delay HCV elimination in many countries (Blach et al., 2021). Disruptions in harm reduction, HCV testing, and HCV treatment services have been observed across Canada (Public Health Agency of Canada, 2020; Van Gennip et al., 2021). In Montreal, HCV incidence among active PWID is high but declining. Nevertheless, our results show that reduced access to HCV services could have reversed this trend. In Germany, models also showed that COVID-19-related disruptions in HCV care may cause an increase in HCV incidence and compromise elimination among men who have sex with men living with HIV (Marquez et al., 2022). Staying on track for HCV elimination will require refocusing public health efforts towards HCV

prevention and care, which may prove difficult in the context of an aggravated overdose crisis (Friesen et al., 2021).

Strengths and limitations

Our results need to be interpreted considering some limitations. First, potential sources of heterogeneity in HCV risks and unmet prevention needs are not explicitly modeled, which could lead to underestimating efforts required for HCV elimination (Baral et al., 2019). For instance, Indigenous peoples, who are disproportionately affected by HCV in Canada, are not explicitly represented (Canadian Network on Hepatitis C, 2019). A minority of PWID self-identify as Indigenous in Montreal, nevertheless, their specific health needs should be addressed (Fayed et al., 2018; Lanièce Delaunay et al., 2022). Second, we assumed that COVID-19-related disruptions in HCV services ceased as of June 2021. Our projections were robust to changes in the scale and duration of these disruptions, yet we may have underestimated the efforts needed to stay on track for HCV elimination by 2030.

Our findings help understand how heterogeneity in HCV acquisition/transmission risk (by HIV status) and needs (between active and ex-PWID) can be factored in the design and implementation of strategies to reduce HCV burden among PWID. These results can inform HCV elimination strategies in settings comparable to Montreal. This is one of few studies to explore the implications of the COVID-19 pandemic on the HCV elimination agenda for priority populations.

Conclusions

In settings with elevated HCV incidence and prevalence, high DAA uptake by all PWID will be required to eliminate HCV as a public health threat among all PWID and PWID living with HIV. Ex-PWID should be included in treatment efforts to avoid preventable HCV-related deaths. The COVID-19 pandemic has impacted HCV prevention and care services for PWID, and concerted efforts to restore and scale-up treatment are urgently needed to ensure that HCV elimination is reached by 2030.

Declarations of Interest

CLD, AG, BL, and CD have no conflict of interest to declare. MK reports grants for investigator-initiated studies from *ViiV Healthcare, Abbvie*, and *Gilead*; research grants from *Janssen*, and consulting fees from *ViiV Healthcare, AbbVie*, and *Gilead*, all outside the submitted work. JC has received institutional funding for investigator-sponsored research from *ViiV Healthcare* and *Gilead Sciences*. He has also received remuneration for advisory work and/or travel support from *ViiV Healthcare, Gilead Sciences* and *Merck Canada*. NK reports research funding from *Gilead Sciences, McGill Interdisciplinary Initiative in Infection and Immunity, Canadian Institutes of Health Research*, and *Canadian Network on Hepatitis C*; reports advisory fees from *Gilead Sciences, ViiV Healthcare, Merck*, and *AbbVie*; and reports speaker fees from *Gilead Sciences, AbbVie*, and *Merck*, all outside of the submitted work. MM-G reports grants from the *Canadian Institutes of Health Research* and the *Canadian Foundation for AIDS Research*, and contractual arrangements from both the *World Health Organization* and the *Joint United Nations Programme on HIV/AIDS* (UNAIDS), all outside of the submitted work.

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Ethical approval

This study was approved by the *McGill University Health center Research Ethics Board* (REB#: MP-37-2019-4700). Our analyses were conducted using publicly available data sources. Hence, consent was not necessary for this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2023.104026.

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