HIV elimination in Québec: tracking progress and evaluating HIV prevention interventions among key populations

Carla Doyle, MScPH

Department of Epidemiology and Biostatistics
McGill University, Montréal

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List of Acronyms and Abbreviations

acquired immunodeficiency syndrome (AIDS)

adjusted odds ratio (aOR)

agent-based (ABM)

Akaike Information Criterion (AIC)

alcohol Use Disorders Identification Test, consumption questions [AUDIT-C]

antiretroviral treatment (ART)

azidothymidine (AZT)

Bayes Information Criterion (BIC)

Canadian AIDS Treatment Information Exchange (CATIE)

confidence interval (CI)

credibility interval (CrI)

degrees of freedom (df)

Federal Non-Insured Health Benefits (NIHB)

gamma hydroxybutyrate (GHB)

gay, bisexual, and other men who have sex with men (gbMSM; GBM)

hepatitis C virus (HCV)

high-incidence risk index (HIRI)

highly active antiretroviral therapy (HAART)

human immunodeficiency virus (HIV)

injectable cabotegravir (CAB-LA)

injection drug use (IDU)

Institut de la statistique du Québec (ISQ)

Institute de santé publique du Québec (INSPQ).

intention-to-treat (ITT)

International Association of Providers of AIDS Care (IAPAC)

Joint United Nations Programme on HIV/AIDS (UNAIDS)

Enquête Québécoise sur la santé de la population (EQSP)

Enquête sur les attitudes et comportements reliés au VIH/sida dans la population générale Québécoise (EHAQ)

latent class analysis (LCA)

leave-one-out cross-validation information criterion (LOOIC)

likelihood ratio (LR)

lysergic acid diethylamide (LSD)

maximum a posteriori estimation (MAP)

men who have sex with men (MSM)

microlitre (μL)

needle and syringe programs (NSP)

New South Wales (NSW)

numéro d'assurance maladie (NAM)

opioid agonist therapy (OAT)

past 6 months (P6M)

past 12 months (P12M)

people living with HIV (PLHIV)

people who inject drugs (PWID)

post-exposure prophylaxis (PEP)

pre-exposure prophylaxis (PrEP)

Public Health Agency of Canada (PHAC)

Régie de l'assurance maladie du Québec (RAMQ)

relative risk reduction (RRR)

respondent-driven sampling (RDS)

respondent driven sampling weights (RDS-II)

sexually transmitted and bloodborne infections (STBBI)

standard deviation (SD)

tenofovir disoproxil fumarate with emtricitabine (TDF/FTC)

treatment-as-prevention (TasP)

undetectable=untransmissible (U=U)

United Nations Human Settlements Programme (UN-Habitat)

United States Food and Drug Administration (FDA)

Watanabe–Akaike information criterion (WAIC)

World Health Organization (WHO)

Abstract

Montréal was Canada's first *UNAIDS Fast-Track City*, aiming to end HIV/AIDS by 2030. The initiative launched with goals for 2020: zero new HIV acquisitions, zero discrimination and stigma, and the 90-90-90 *UNAIDS* care cascade targets (90% of people living with HIV [PLHIV] diagnosed; of those, 90% on antiretroviral treatment [ART]; and, of those, 90% virally suppressed; advancing to 95-95-95 by 2025). Meeting these targets requires understanding current epidemics and prevention needs among key populations most vulnerable to HIV acquisition and transmission. My thesis informs HIV elimination by evaluating prevention use in gay, bisexual, and other men who have sex with men (gbMSM) and strengthening epidemic monitoring in gbMSM and people who inject drugs (PWID) in Québec.

My first thesis question sought to identify and characterize prevention patterns in Montréal gbMSM and their associated determinants in the pre-exposure prophylaxis (PrEP) era. Applying latent class analysis to representative 2017-2018 survey data stratified by HIV serostatus, I uncovered patterns (classes) of similar prevention users –three among PLHIV and four among those whose HIV-status was negative or unknown. Within each class, usage of different types of prevention was limited. While condoms were a mainstay, antiretroviral prevention was also used. Treatment-as-prevention appeared fundamental to all classes of PLHIV and PrEP was central to a small biomedical use class. With multinomial logistic regression, I compared the various identified prevention classes (where either condoms, seroadaptive behaviours, and biomedical strategies are central) to participants using fewer prevention strategies. I found that those in the condom, seroadaptive behaviour, and biomedical prevention classes had more anal sex partners. In those whose HIV-status was negative/unknown, those classes were also more likely to be recently diagnosed with a sexually transmitted infection. Another result was that belonging to the PrEP and other biomedical use class was associated with higher education.

Secondly, I evaluated the population-level effectiveness of PrEP on sexual HIV transmission in Montréal gbMSM over 2013-2021. Using an agent-based mathematical model, I simulated PrEP use and counterfactual scenarios, estimating the annual and

cumulative fractions of HIV acquisitions averted. I found that, given PrEP's low coverage until 2015, few acquisitions were initially averted, but that number started increasing in 2017. In 2019 coverage peaked when 10% of all gbMSM with an HIV-negative serostatus were currently on PrEP. In that year, 36% of acquisitions were averted (90% credibility interval [CrI]: 22%-48%). Afterward, this level of impact persisted despite coverage being affected by the COVID-19 pandemic. Cumulatively, excluding 2013-2014, PrEP prevented 20% (90%CrI: 11%-30%) of HIV acquisitions. If Montréal's PrEP coverage had reached a level like that observed in Vancouver, where PrEP is provided free-of-charge to eligible gbMSM, up to 63% (90%CrI: 54%-70%) of HIV acquisitions could have been averted over 2015-2021.

Lastly, I estimated the number of new HIV acquisitions for two key populations by year and geographical area. To benchmark and monitor elimination, I developed a mathematical model synthesizing surveillance data to estimate HIV incidence in Québec gbMSM and PWID. It is an age-stratified, multi-state, back-calculation Bayesian model estimating incidence, prevalence and the care cascade by geography, key population, and age. My results showed important incidence declines and progress in diagnosis and care in gbMSM and PWID (<10% undiagnosed, time from acquisition-to-diagnosis <2 years, and high ART coverage in 2020). However, the 2020 target of zero new HIV acquisitions was not met. That year, there were an estimated 266 (95%CrI: 103-508) new HIV acquisitions among gbMSM and 6 (95%CrI:1-26) among PWID in Québec, of which 97 (95%CrI: 33-227) and 2 (95%CrI: 0-14), respectively, were acquired in Montréal. Additionally, slightly higher fractions of PLHIV were undiagnosed outside of Montréal, as well as in young gbMSM.

Québec has made strides in addressing HIV and more work is needed. My thesis showed that unmet prevention needs remain, especially for gbMSM. PrEP is not achieving its full potential and barriers to access should be addressed: eligible gbMSM are not accessing it, and this limited its benefits in preventing new HIV acquisitions. Also, while I showed that those that adopted PrEP by 2018 had higher education, identifying further disparities and barriers to PrEP access is important. Differences in HIV status awareness need to be overcome by further prioritizing testing in young gbMSM and ensuring adequate access to

such services outside urban centres. As the prevention landscape and epidemic drivers continue to evolve, monitoring the epidemic will remain critical, and the models developed in my thesis provide the epidemic intelligence to do so.

Résumé

Montréal a été la première *Ville de l'initiative Fast-Track de l'ONUSIDA* au Canada, visant à mettre fin au VIH/sida d'ici 2030. L'initiative a été lancée avec des objectifs pour 2020 : zéro nouvelle acquisition de VIH, zéro discrimination et stigmatisation, ainsi que les cibles de la cascade de soins 90-90-90 de l'ONUSIDA (90% de personnes vivant avec le VIH (PVVIH) diagnostiquées; parmi celles-ci, 90% sous traitement antirétroviral (TAR); et, parmi celles-ci, 90% ayant une charge virale supprimée; passant à 95-95-95 d'ici 2025). Pour y répondre, il faut comprendre les épidémies actuelles et renforcer la prévention pour les populations clés les plus vulnérables à l'acquisition et à la transmission du VIH. Ma thèse apporte un éclairage sur l'élimination du VIH. Elle évalue l'utilisation de la prévention chez les hommes ayant des relations sexuelles avec des hommes (HARSAH) et renforce la surveillance épidémique chez les HARSAH et les personnes qui s'injectent des drogues (UDI) au Québec.

Pour y arriver, j'ai d'abord identifié les méthodes de prévention chez les HARSAH montréalais et décrit leurs facteurs associés. En appliquant l'analyse des classes latentes aux données de l'enquête populationnelle de 2017-2018, stratifiées par statut sérologique VIH, j'ai découvert des classes d'utilisateurs de prévention similaires. Dans chacun, l'utilisation de différents types de prévention était limitée. Alors que l'utilisation des préservatifs demeurent une pratique courante, la prévention antirétrovirale est devenue accessible. Le traitement antirétroviral comme prévention semblait fondamental pour toutes les classes de PVVIH et la PrEP était centrale pour une petite classe d'utilisation biomédicale. Par régression logistique multinomiale, j'ai comparé les classes les moins utilisées à celles définies par les types de prévention (préservatif, comportement séroadaptatif et biomédical). J'ai trouvé que ceux dans les classes de prévention avaient plus de partenaires sexuels anaux. Ceux dont le statut VIH était négatif/inconnu, étaient également plus susceptibles d'avoir récemment reçu un diagnostic d'infection sexuellement transmissible. Aussi, l'appartenance à la classe PrEP et autres usages biomédicaux était associée à un plus haut niveau d'instruction.

Deuxièmement, j'ai utilisé un modèle mathématique à base d'agents qui simule les dynamiques de transmission sexuelle du VIH chez les HARSAH pour évaluer l'efficacité de la PrEP au niveau de la population à Montréal entre 2013-2021. J'ai simulé une intervention PrEP et des scénarios contrefactuels, en estimant les fractions annuelles et cumulées des acquisitions évitées de VIH. Avec une faible couverture de la PrEP jusqu'en 2015, peu d'acquisitions ont été initialement évitées, mais leur nombre a commencé à augmenter en 2017. En 2019, la couverture a culminé à 10% et 36% des acquisitions ont été prévenues (intervalle de crédibilité à 90%[CrI]: 22%-48%). Ce niveau d'impact a persisté malgré la pandémie de COVID-19. Cumulativement, à l'exclusion de 2013-2014, la PrEP a empêché 20% (90%CrI: 11%-30%) des acquisitions du VIH. Cependant, si Montréal avait atteint le même niveau de couverture PrEP que Vancouver, où elle est gratuite aux HARSAH éligibles, jusqu'à 63% (90%CrI: 54%-70%) des acquisitions qui auraient pu être prévenues (2015-2021).

Enfin, pour comparer et surveiller l'élimination, j'ai développé un modèle mathématique synthétisant les données de surveillance provinciale pour estimer l'incidence du VIH chez les HARSAH et les personnes UDI du Québec. Il s'agit d'un modèle bayésien multi-états et rétro-calculé stratifié par âge qui estime l'incidence, la prévalence et la cascade de soins par aire géographique, population clé et âge. Mes résultats ont montré une baisse importante de l'incidence et des progrès notables pour le diagnostic et la cascade de soins chez les HARSAH et les personnes UDI (<10 % non diagnostiqués, <2 ans entre l'acquisition et le diagnostic et couverture élevée du TAR en 2020). Cependant, l'objectif de zéro acquisition pour 2020 n'a pas été atteint. Cette année-là, j'estimais à 266 (95%CrI: 103-508) acquisitions chez les HARSAH et 6 (95%CrI: 1-26) chez les personnes UDI au Québec, dont 97 (95%CrI: 33-227) et 2 (95%CrI: 0-14) ont été acquises à Montréal. De plus, des fractions légèrement plus élevées de PVVIH n'ont pas été diagnostiquées à l'extérieur de Montréal, ainsi que chez les jeunes HARSAH.

Le Québec continue de progresser dans sa lutte contre le VIH. Néanmoins, ma thèse a démontré que des besoins de prévention non satisfaits subsistent, en particulier pour les HARSAH. La portée de la PrEP pourrait notamment être élargie –il y a des HARSAH éligibles mais qui n'y ont pas accès, ce qui a limité ses bénéfices. De plus, alors que j'ai

montré que les premiers utilisateurs avaient fait des études supérieures, il est essentiel d'identifier davantage les disparités et les obstacles à l'accès à la PrEP. Les différences de couverture de diagnostic doivent également être surmontées en accordant davantage la priorité au dépistage chez les jeunes HARSAH et en garantissant un accès adéquat à ces services en dehors des centres urbains. À mesure que le paysage de la prévention et les moteurs de l'épidémie évoluent, la surveillance de l'épidémie restera essentielle, et les modèles développés dans ma thèse fournissent l'information stratégique pour y arriver.

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Statement of Originality

The work presented in this thesis constitutes original scholarship and contributes to the knowledge base of HIV epidemiology and prevention programming in the city of Montréal and the province of Québec. Manuscript 1 updated our understanding of how gbMSM in Montréal are combining different HIV prevention strategies in the PrEP era and identified characteristics associated with derived patterns of use. Manuscript 2 evaluated the population-level impact of PrEP among gbMSM in Montréal, something that has yet to be done in a Canadian setting. Moreover, few such evaluations of PrEP have been performed elsewhere, and these faced some limitations that I was able to address in the mathematical model used to complete my study. Lastly, Manuscript 3 provided robust estimates of HIV elimination targets by assessing HIV incidence trends and other epidemic metrics among gbMSM and PWID across Québec and in Montréal. Using a mathematical model to obtain these estimates helped overcome challenges in estimating transmission metrics in a low incidence setting.

In addition to the papers presented in this thesis, I co-authored four articles during my doctorate on topics ranging from HIV testing to hepatitis C transmission. These are included below for reference:

Published

- Maheu-Giroux M, Marsh K, **Doyle CM**, Godin A, Lanièce Delaunay C, Jonhson LF, Jhan A, Abo K, Mbofana F, Boily MC, Buckeridge DL, Hankins C, and Eaton JW (2019). National HIV testing and diagnosis coverage in sub-Saharan Africa: a new modeling tool for estimating the "first 90" from program and survey data. *AIDS* 2019 33(Suppl. 3):S255-S259.

- Milwid R, Xia Y, **Doyle CM**, Cox J, Lambert G, Thomas R, Mishra S, Grace D, Lachowsky NJ, Hart TA, Boily MC, and Maheu-Giroux M (2022). Past dynamics of HIV transmission among men who have sex with men in Montréal, Canada: a mathematical modeling study. *BMC Infectious Diseases* 22:233. (doi.org/10.1186/s12879-022-07207-7).

Accepted

- Lanièce Delaunay C, Klein MB, Godin A, Cox J, Kronfli N, Lebouché B, **Doyle CM**, Maheu-Giroux M (2022). Public health interventions, priority populations, and the impact of COVID-19 disruptions on hepatitis C elimination among people who have injected drugs in Montréal (Canada): a modeling study.

- Stansfield S, Heitner J, Mitchell K, **Doyle CM**, Milwid R, Moore J, Donnell D, Hanscom B, Xia Y, Maheu-Giroux M, Van de Vijver D, Wang H, Barnabas R, Boily MC, Dimitrov D (2023). Population-level impact of expanding PrEP coverage by offering long-acting injectable PrEP to MSM in three high resources settings: a model comparison analysis.

Contributions of Authors

Manuscript 1: Carla M Doyle, Mathieu Maheu-Giroux, Gilles Lambert, Sharmistha Mishra, Herak Apelian, Marc Messier-Peet, Joanne Otis, Daniel Grace, David M Moore, Nathan Lachowsky, Joseph Cox**.** Combination HIV Prevention Strategies Among Montréal Gay, Bisexual, and Other Men Who Have Sex with Men in the PrEP Era: A Latent Class Analysis. *AIDS and behavior*. 2021;25(1):269-83.

I conceptualized this study with my supervisors, Dr. Mathieu Maheu-Giroux and Dr. Joseph Cox, as part of a fellowship with the *Engage* study. With their guidance, I established the research question, developed the methodological protocol, performed all analyses, interpreted the results, and drafted the manuscript. Dr. Joseph Cox, Dr. Gilles Lambert, Dr. Daniel Grace, Dr. David M Moore, and Dr. Nathan Lachowsky are co-principal investigators of the *Engage* study. Herak Apelian and Marc Messier-Peet were research coordinators and assistants with the Montréal *Engage* study team whose responsibilities included participant recruitment, questionnaire development, and data management and analyses. Dr. Sharmistha Mishra (my thesis committee member) and Dr. Joanne Otis are collaborators of the *Engage* study and provided critical feedback based on their methodological and content expertise. All authors provided input on the measures examined in the study, aided in interpreting the results, and reviewed the manuscript for submission and during the peer-review process.

Manuscript 2: Population-level impact of pre-exposure prophylaxis on HIV acquisition and transmission among men who have sex with men: a mathematical modeling study in Montréal, Canada (2013-2021). Carla M Doyle, Rachael M Milwid, Joseph Cox, Yiqing Xia, Gilles Lambert, Cécile Tremblay, Joanne Otis, Marie-Claude Boily, Jean-Guy Baril, Réjean Thomas, Alexandre Dumont Blais, Benoit Trottier, Daniel Grace, David M. Moore, Sharmistha Mishra, Mathieu Maheu-Giroux. *To be submitted.*

This study was conceptualized by Dr. Mathieu Maheu-Giroux and funded by the Canadian Institute of Health Research (CIHR). Dr. Joseph Cox, Dr. Gilles Lambert, Dr. Cécile Tremblay, Dr. Joanne Otis, Dr. Marie-Claude Boily, Dr. Jean-Guy Baril, Dr. Réjean Thomas, Dr. Benoit Trottier, and Dr. Sharmistha Mishra were co-applicants, and I was a

collaborator on the CIHR grant proposal. Building on the proposal, Dr. Rachael M Milwid, Yiqing Xia, and I built, parameterized, and calibrated the mathematical model of HIV transmission. I was fully responsible for developing the PrEP module, provided critical input to other model domains, and calibrated the model together with Dr. Rachael M Milwid. This model has since been used for multiple purposes and was adapted by the *Public Health Agency of Canada* to inform the response to the 2022 mpox outbreak. For this manuscript, under the guidance of Dr. Mathieu-Giroux and Dr. Joseph Cox, I performed all model analyses, interpreted the results, and drafted the manuscript. Dr. Joseph Cox, Dr. Gilles Lambert, Dr. Daniel Grace, and Dr. David M. Moore are co-principal investigators of the *Engage* study, which was used to parameterize and calibrate the model. All authors contributed to the interpretation of results and reviewed the manuscript for submission.

Manuscript 3: Carla M Doyle, Joseph Cox, Rachael M Milwid, Raphaël Bitera, Charlotte Lanièce Delaunay, Michel Alary, Gilles Lambert, Cécile Tremblay, Sharmistha Mishra, Mathieu Maheu-Giroux. Measuring progress towards reaching zero new HIV acquisitions among key populations in Québec (Canada) using routine surveillance data: a mathematical modeling study. *Journal of the International AIDS Society*. 2022;25(9):e25994.

I conceptualized this study with my supervisors, Dr. Mathieu Maheu-Giroux, and Dr. Joseph Cox. Together, we developed the research question and designed the mathematical model. With their guidance, I built, parameterized, and calibrated the model, performed model analyses, interpreted the results, and drafted the manuscript. Dr. Rachael M Milwid, Dr. Charlotte Lanièce Delaunay, and Dr. Sharmistha Mishra were consulted for their expertise in HIV modeling. Dr. Raphaël Bitera, Dr. Michel Alary, and Dr. Gilles Lambert are affiliated with the *Institute de santé publique du Québec* and were involved in collecting the HIV surveillance data used to calibrate the model. Dr. Cécile Tremblay was consulted for her expertise in HIV research, PrEP, and surveillance in Québec. All authors provided feedback on the study methodology, contributed to the interpretation of results, and reviewed the manuscript for submission and during the peer-review process.

Chapter 1. Introduction

1.1. Background

More than 40 years after the human immunodeficiency virus (HIV) was established as a pandemic, it remains a major global health concern for which no vaccine or cure exists. Throughout this time, great strides have been made, from dynamic community responses to new therapeutics and addressing stigma and discrimination. Today, various biomedical, behavioural, and structural prevention strategies can be used and combined for effective protection against HIV transmission and acquisition. Still, 1.5 million new HIV acquisitions occurred globally in 2021[1, 2]. Furthermore, despite the absence of a cure for HIV, antiretroviral therapy (ART) halts disease progression in people living with HIV (PLHIV), making the progression to acquired immunodeficiency syndrome (AIDS) entirely preventable. ART can also reduce the amount of virus in the blood of PLHIV to the point that it is undetectable. Once it reaches that stage, the risk of transmission from PLHIV is zero[3]. However, important barriers to treatment access and use leave millions of PLHIV untreated or with detectable viral load levels[1, 2]. In 2021, these treatment gaps led to an estimated 650,000 deaths from AIDS-related causes[1, 2].

The *Joint United Nations Programme on HIV/AIDS* (UNAIDS) set forward ambitious goals of Ending the AIDS Epidemic in 2014[4]. The initial objective was to achieve the 90-90-90 targets by 2020. These targets call for 90% of PLHIV to be aware of their status, 90% of those aware to receive ART, and 90% of those on ART to have a suppressed viral load. In 2020, UNAIDS released a new set of targets that United Nations Members States adopted in 2021 as part of the new *Political Declaration on HIV and AIDS*[5]. The new goals set the three preceding targets to 95% by 2025. Countries and regions worldwide have endorsed and accelerated progress towards these targets, Canada included[6]. Nevertheless, the 2020 targets were not met globally[6]. Even in countries that achieved them, some populations were left behind[6]. Progress was also slowed during 2020-2021 due to COVID-19 pandemic disruptions[2, 6].

Prompted by the 2021 *Political Declaration on HIV and AIDS*, UNAIDS developed the *HIV Prevention 2025 Road Map*, guiding countries through steps of programme

assessment, implementation, and scale-up to ensure they are large-scale, focused on high-impact and high-quality interventions, and are delivered equitably[3]. The map is based on five prevention pillars, two of which apply globally. The first is that key populations, whose unmet prevention needs put them at increased risk of HIV acquisition and transmission, must receive tailored prevention services that are accessible and discrimination-free[3]. In Canada, such key populations include gay, bisexual, and other men who have sex with men (gbMSM), people who use injection drugs (PWID), transgender women, people with experience of incarceration, indigenous peoples, and migrants. The second is that antiretroviral-based prevention, namely, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) and treatment-as-prevention, must be prioritized in combination HIV prevention programs[3].

Canada's current HIV response is guided by its national framework and five-year action plan against sexually transmitted and bloodborne infections (STBBI) developed by the *Public Health Agency of Canada* (PHAC) in 2019[7, 8]. This action plan does not yet outline specific targets. However, like others, it emphasizes the reduction of STBBI incidence, including HIV; improvements in STBBI prevention and access to diagnosis, treatment, and care; and addressing stigma and discrimination that increase vulnerabilities to STBBI acquisition[8].

More formal commitments to HIV elimination have been made by provincial and municipal governments across Canada. Cities are crucial players in HIV elimination because they are often home to key populations[9]. The city of Montréal took the lead in solidifying its commitment to HIV elimination. In 2017, it became the country's first *Fast-Track City*, an HIV elimination initiative engaging cities internationally in partnership with UNAIDS, the *International Association of Providers of AIDS Care* (IAPAC), the *United Nations Human Settlements Programme* (UN-Habitat), and the City of Paris[10-12]. By signing the *Paris Declaration on Fast-Track Cities*, Montréal committed to HIV elimination by 2030, not only by setting the 90-90-90 and 95-95-95 targets outlined above but also by reaching zero new HIV acquisitions and zero HIV discrimination and stigma in 2020[12, 13].

This thesis examines the HIV epidemics among gbMSM and PWID in the province of Québec. These two populations have historically faced vulnerabilities that perpetuate their increased risk of HIV acquisition and transmission. My overarching objective is to inform the path forward to eliminate HIV among two priority populations and, ultimately, to support the provincial and national HIV responses. To achieve this goal, I seek to document and monitor the epidemics, understand the current prevention landscape for gbMSM, and evaluate the impact of a biomedical intervention to reduce HIV acquisitions.

1.2. Organization of this thesis

This manuscript-based thesis is articulated around three research objectives, as follows:

1. To assess patterns in the use of PrEP and other HIV prevention strategies among Montréal gbMSM and described the potentially important factors associated with observed patterns.

2. To evaluate and explored the population-level effectiveness of PrEP intervention on the HIV epidemic among gbMSM in Montréal using a mathematical model.

3. To estimate the annual incidence of HIV among gbMSM and PWID in Montréal and Québec overall using a back-calculation mathematical model that synthesized provincial surveillance data.

The thesis is comprised of three manuscripts, each addressing the research objectives stated above. Before presenting the manuscripts, chapters containing necessary supporting information are presented. Chapter 2 includes a literature review that highlights the evidence and knowledge gaps addressed by my three objectives. Chapter 3 provides an overview of the data sources and types of models used in my thesis research. The three thesis objectives are then addressed (Chapters 4-7). Specifically, in Chapter 4, I assess patterns in PrEP use and other HIV prevention strategies among Montréal gbMSM and describe the factors associated with the observed patterns. In Chapter 5 I evaluate the population-level effectiveness of PrEP on the HIV epidemic among Montréal gbMSM using an agent-based mathematical model of sexual HIV transmission. In Chapter 6 I

develop a mathematical model that synthesizes surveillance data to estimate the annual incidence of HIV to benchmark and monitor elimination efforts among gbMSM and PWID in Montréal and Québec. Finally, Chapter 7 synthesises the manuscript results, interprets the findings in the larger context of HIV elimination efforts, and provides some guidance to achieve it.

Chapter 2. Literature Review

2.1. HIV's natural history and treatment

HIV is a retrovirus acquired through the body's mucosal membranes or via direct injection into the bloodstream. Once the virus is acquired, it fuses with and destroys the CD4 cells in the blood during viral replication[14]. These cells are central players in the immune system's response to external pathogens. Without treatment, the number of CD4 cells in those who have acquired HIV will decline gradually over time, damaging the immune system, causing immunosuppression, and eventually leading to AIDS and death.

Three main stages characterize the course of an HIV infection: the acute (or primary) infection, a chronic infection phase, and AIDS[14]. During acute infection, the virus replicates rapidly, sometimes causing non-specific 'flu-like' symptoms[14-16]. The transition into chronic infection, where viral replication has slowed and stabilized, occurs after an average of 3 months and can last upwards of 6-10 years if left untreated[17-19]. Throughout this stage, PLHIV remain mostly asymptomatic. However, the disease's progression and impact on the immune system can be monitored and proxied by the CD4 cell count per microlitre of blood (μL). This count can decline from over 500 cells/μL to approximately 200 cells/μL before the onset of AIDS[14]. At this stage, the depletion of CD4 cells continues, and the risk of opportunistic infections increases, causing severe illness and, ultimately, death.

The toll of HIV infection and AIDS, in terms of morbidity and mortality, was high in the early phases of the pandemic: there was no effective treatment for HIV infection, and only opportunistic infections could be addressed[20]. In 1987, the first antiretroviral drug for HIV, azidothymidine (AZT; also called zidovudine and branded as Retrovir)[21], was shown to be effective in blocking viral replication[22] and was rapidly approved by the US Food and Drug Administration (FDA)[23, 24]; it subsequently became accessible in Canada that year[25]. While preventing AIDS-related deaths and opportunistic infections[26], AZT monotherapy quickly led to drug resistance among its users, necessitating the use of multiple antiretroviral drugs targeting different phases of the viral replication process[14, 20, 21]. These medications became available over time and HIV treatment was revolutionized in 1996 through the introduction

of highly active antiretroviral therapy (HAART), combining several medications to avert poor health outcomes[14, 20]. When taken consistently, HAART reduces HIV's viral load and the likelihood of drug resistance, allowing CD4 cells to replenish and improve the immune system[14]. Thus, HAART halts disease progression, and the life expectancy of PLHIV receiving HAART (hereafter referred to as antiretroviral treatment or ART) is now considered similar to those not living with HIV[27-30].

Further to the treatment evolution from AZT to HAART was research demonstrating the health benefits of treating PLHIV at earlier stages of infection and its efficacy in preventing transmission, all of which prompted changes in recommendations for use[31]. Initially, upon HAART availability in 1996, treatment guidelines indicated use by PLHIV with a CD4 cell count ≤350 cells/μL to prevent disease progress and death from AIDS[32-34]. Later evidence showed improved health outcomes with earlier ART initiation and that PLHIV on ART with a suppressed viral load could not transmit HIV[35-40]. In 2013, organizations began recognizing these research findings, implementing guideline changes that increased ART access by recommending use among PLHIV with a CD4 cell count ≤500 cells/μL[32, 41]. Soon after, in 2016, clinical guidelines recommended ART for all PLHIV regardless of their CD4 cell count[41].

2.2. HIV's modes of transmission

HIV can be found in the blood, semen, vaginal fluids, and breast milk of PLHIV. It can be transmitted and acquired through multiple anatomical sites: 1) cervicovaginal, penile, rectal, or oral and other mucous membrane sites, 2) in-utero, 3) percutaneously, or 4) intravenously[14, 16, 42]. Epidemiologically, the primary mode of HIV transmission is sexual. However, iatrogenic, injection drug use, blood transfusions (especially plasma), and mother-to-child transmission are also important modes of transmission. The probability of transmission varies by mode (e.g., higher from intravenous modes vs sexual) and sites of contact (i.e., receptive anal vs receptive vaginal sex). Transmission probabilities also vary as a function of viral load. During the acute phase of infection, the HIV antibody response is still developing, and the viral load increases rapidly. Thus, transmission in that stage is an estimated 5.3 (95% credibility interval [CrI]: 0.79–57) times higher than during the

chronic stage[43]. The chronic stage is characterized by a stable viral load, which begins to increase again in late-stage disease, albeit at a slower rate[15]. During the 10-19 months before death from AIDS, HIV transmissibility is approximately seven times higher than in the chronic stage[17]. However, the symptomatic nature of this phase also often results in fewer sexual contacts[44].

2.3. HIV/AIDS epidemiology in Canada and Québec

The HIV epidemic in Canada has disproportionally impacted and remained highly concentrated in key populations. The country's epidemic took hold among gbMSM. AIDS was first identified in Canada when a man from this population was reported to have died from AIDS in 1982[45]. By mid-1985, gbMSM accounted for 70% of the 248 reported AIDS cases[46]. Fast-forwarding to 2020, of the estimated 1,520 (range: 870-2,260) people that acquired HIV nationally that year, 44% were gbMSM (Figure 2.3.1)[47]. PWID were another population impacted early in the epidemic that remains at increased risk, composing 20% of the estimated HIV acquisitions in 2020 (Figure 2.3.1)[47]. Other groups, such as indigenous peoples, people with experience in Canada's prison system, and transgender women, are among those also impacted by HIV across the country today.

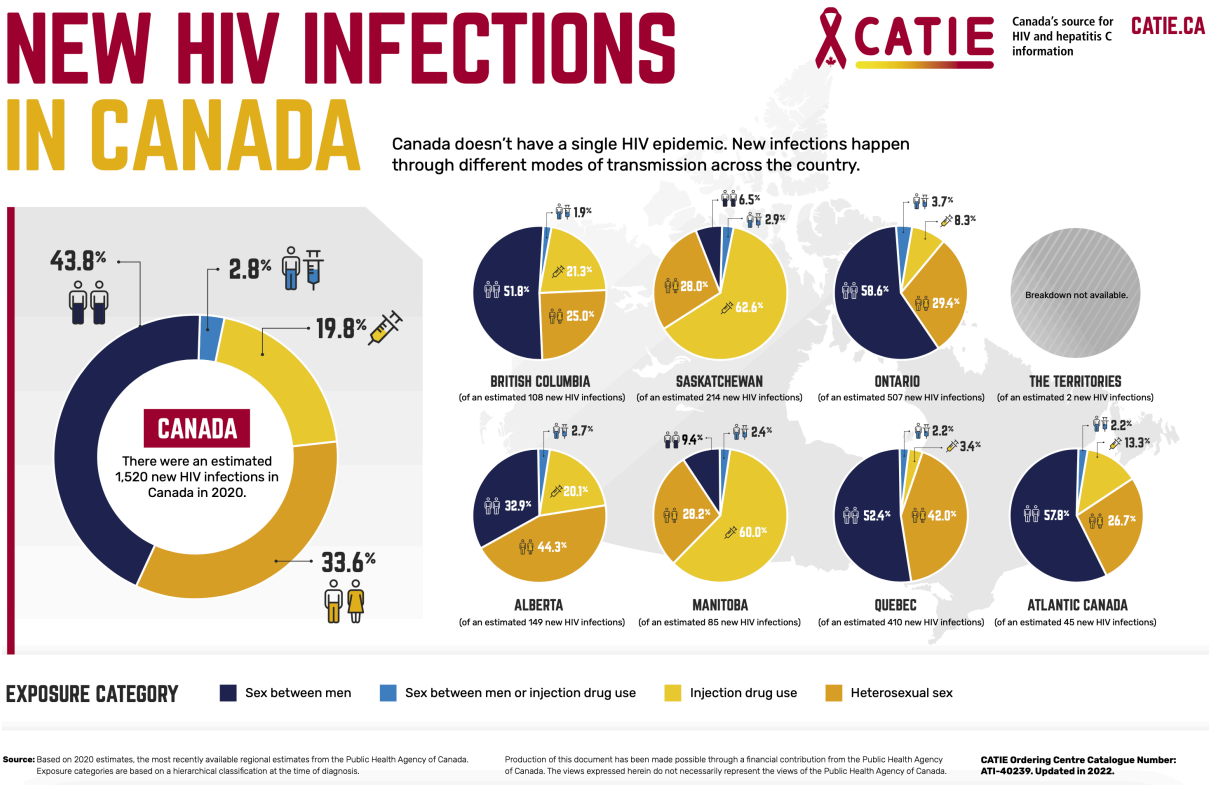

Figure 2.3.1. Estimated proportions of HIV acquisitions acquired by key populations in Canada in 2020.

This infographic is reproduced from CATIE (Canadian AIDS Treatment Information Exchange) under a Creative Commons Attribution Licence 2.0[48].

HIV incidence peaked among Canadian gbMSM and PWID in the mid-to-late-1980s[49, 50]. Subsequently, the highest number of annual reported AIDS cases followed in the early-to-mid 1990s[51]. However, with declining incidence and the introduction of HAART, by the mid-to-late 1990s, the number of AIDS diagnoses and AIDS deaths in the country strikingly reduced[51]. While a second, lower spike was estimated to have occurred among gbMSM in the early 2000s[49, 50], the number of incident HIV acquisitions estimated over 2011-2018 for both gbMSM and PWID has been relatively stable[51-53]. Correspondingly, HIV prevalence has continued increasing in gbMSM and PWID. Of the estimated 62,790 (range: 55,200-70,300) PLHIV in Canada, approximately 50% were gbMSM (N=31,589, range: 27,000-36,000), and 13% were PWID (N=8,338, range: 7,100-9,500)[47].

Provincially, Québec has consistently been among the provinces with the highest HIV burden[51]. In 2020, 27% of acquisitions occurred in Québec, and 28% of Canada's PLHIV were residing there –the second highest proportion after Ontario[47]. Despite this, the provincial breakdown of new acquisitions by key population differs somewhat from the national picture (Figure 2.3.1). While the proportion of those acquired by gbMSM in Québec is estimated to be slightly higher (52% in Québec compared to 44% nationally), the proportion acquired by PWID is much lower than the national estimate (3% in Québec compared to 20% nationally)[47]. Within Québec, the Montréal metropolitan region stands as the epicentre, with a diagnosis rate of 5.6 per 100,000 population in 2020, one of the highest nationally[54, 55].

2.4. Individual-based strategies for preventing sexual HIV transmission in gbMSM

Early in the HIV pandemic, even before AIDS was characterized, PLHIV and gbMSM community organizations were at the forefront of prevention, creating promotional materials on *potential* risk behaviours such as receptive anal sex and oral-anal sex (i.e., rimming) and safer sex practices[56-58], including condom use (although condoms had yet to be shown effective for HIV prevention, they were already recognized as effective tools for preventing the transmission of other STBBIs), hygienic (e.g., washing with soap and water before and after sex), and others (e.g., obtaining contact information of sex partners or negotiating sex acts)[56-58]. By 1986, with the confirmation that HIV caused AIDS, that modes of HIV transmission included sex, and that condoms were effective for HIV prevention[59], condom use became the predominant prevention strategy promoted for gbMSM[60-62]. HIV antibody testing was also available in 1985, allowing PLHIV to become aware of their status[25]. This gave way to seroadaptive behavioural strategies[63-69] like serosorting (choosing sex partners based on HIV serostatus) and strategic positioning (choosing the receptive or insertive anal sex position based on HIV serostatus), which rely on knowledge and disclosure of HIV status. These early strategies were the mainstay of combination HIV prevention until the 2000s and are still commonly practiced today.

Starting in 2001, with the introduction of HIV-PEP, antiretrovirals have been available and promoted for HIV prevention. PEP, which can reduce the risk of HIV acquisition by 80%, involves taking antiretrovirals for 28 days within 48 hours of a potential HIV exposure[70, 71]. By the end of that decade, the notion of treatment-as-prevention was widely known and discussed. It was first proposed as a strategy in 2006 by researchers from Vancouver, Canada, in what is now seen as a landmark viewpoint[72, 73]. Based on available observational data and demographic and mathematical models, Montaner et al. suggested that expanding access and providing ART to all diagnosed PLHIV had the potential to end the HIV pandemic[72]. Subsequently, the first formal recommendation for treatment-as-prevention was made in 2008 by the *Swiss Federal Commission for AIDS-related Issues*[74, 75]. In its *Swiss HIV Statement*[74, 75], the commission recognized that, while the magnitude had yet to be determined in a trial setting, it was already clear that the risk of HIV transmission from PLHIV with a suppressed viral load was negligible[75]. Finally, in 2011, trial results arrived –the HPTN052 trial showed that ART undoubtedly prevented HIV transmission, estimating a 96% reduction in HIV incidence among serodiscordant couples[35]. Several other trials further confirmed this[36-40]. Thus, treatment-as-prevention (coined as TasP) became the first antiretroviral-based strategy to arise as a game-changer in the HIV prevention landscape.

The second antiretroviral-based strategy thought of in this manner was HIV-PrEP, an antiretroviral medication that can be taken by individuals who do not have HIV but are at high risk of acquiring it[76, 77]. Research on PrEP began with animal studies in the late 1990s[78-80], advancing to human trials in the early 2000s. Beginning with results from the iPrEx trial in 2010, oral tenofovir disoproxil fumarate with emtricitabine (TDF/FTC) has proven to be efficacious across various subpopulations at-risk for HIV acquisition. Among gbMSM, the oral TDF/FTC efficacy estimates of daily and on-demand use that emerged ranged from 44%-97% (Table 2.4.1). However, PrEP efficacy is highly dependent on adherence[81]. For example, the intention-to-treat (ITT) estimate of relative risk reduction (RRR) from the iPrEX trial was 44% (95%CI: 15%–63%), the lowest of all trials, but the assessment of drug levels in participant plasma samples found only 51% of participants had detectable drug levels, and thus, low adherence to the study protocol of daily use[82]. When comparing those with detectable drug levels to those without, the estimated RRR

was substantially higher, at 92% (95%CI: 40-99%)[82]. Notably, the IPERGAY trial was conducted among gbMSM in Montréal and France. In 2013, after 9.3 months, the trial was terminated early, finding an 86% RRR in HIV infection rates among gbMSM assigned to on-demand (also referred to as "intermittent" or "event-level") oral PrEP compared to placebo[76, 77]. An open-label extension study of IPERGAY further showed a RRR in HIV incidence among fully-adherent oral PrEP users of 97% (95%CI: 81%-100%)[77].

Table 2.4.1. Efficacy estimates of oral TDF/FTC among gbMSM

Authors (Year)	Design	Regimen	Efficacy (95%CI)
Grant et al. (2010)[82]	RCT (iPrEx)	Daily	44% (15%–63%)
Anderson et al. (2012)[83]	Pharmacokinetic (iPrEx sub study)	2 doses/week 4 doses/week 7 doses/week	76% (56%–96%) 96% (90%–>99%) 99% (96%–>99%)
Seifert et al. (2015)[84]	Pharmacokinetic	after 1 dose after 3 doses after 5 doses after 7 doses discontinuing on day 30	77% (40%–93%) 96% (60%–100%) 99% (69%–100%) 99% (70%–100%) >90% for 7 days
Molina et al. (2015)[76]	RCT (IPERGAY)	On-demand	86% (40%–98%)
McCormack et al. (2016)[85]	Pragmatic trial (PROUD)	Daily	86% (64%–96%)
Molina et al. (2017)[77]	Cohort (IPERGAY extension study)	On-demand	97% (81%-100%)

In 2012, the World Health Organization (WHO) released guidelines on PrEP use for serodiscordant couples and gbMSM and transgender women at high risk of HIV acquisition[86]. Around the same time, the FDA granted the first approval of oral TDF/FTC, indicating use for adults at high risk of HIV acquisition[87, 88]. Since then, PrEP guidelines have evolved[89, 90], jurisdictions have continued approving PrEP, and access has been expanding[2]. Moreover, long-acting modalities of PrEP that are injectable or implantable are in the pipeline. In fact, long-acting injectable cabotegravir (CAB-LA) has already been found more efficacious than oral PrEP in cisgender gbMSM and transgender women who have sex with men (66% [95%CI: 38-82%] RRR in HIV incidence among those assigned

to CAB-LA compared to those assigned to oral TDF/FTC)[91, 92] and cisgender women[93, 94] at-risk for HIV and, in 2021, was approved by the US FDA[95].

2.5. Current paradigms in HIV prevention programming

There are no vaccines for HIV, and available treatments cannot cure PLHIV of the virus. Therefore, control of the HIV epidemic hinges on prevention. No single prevention strategy can, alone, eliminate HIV. Leveraging synergies and combining structural, biomedical, and behavioural interventions targeting different risk factors on the transmission pathway is recommended to improve HIV control program impacts and reduce HIV transmission[96-98]. This concept, known as combination HIV prevention, has remained the foundation of HIV prevention programming since 2003[96]. However, the make-up and delivery of combination HIV prevention programs are dynamic. The emergence of antiretroviral-based strategies, in particular, has prompted a paradigm shift in the approach to HIV prevention and care delivery towards one which is '*status-neutral*' (Figure 2.5.1)[99, 100]. The premise is that now, anyone can be engaged in care for HIV-related services, regardless of their serostatus, and that the steps to engagement and retention in care can stem from the same branch. Thus, it is increasingly relevant for program assessments or attempts at understanding the HIV prevention and care landscape to adopt a status-neutral lens.

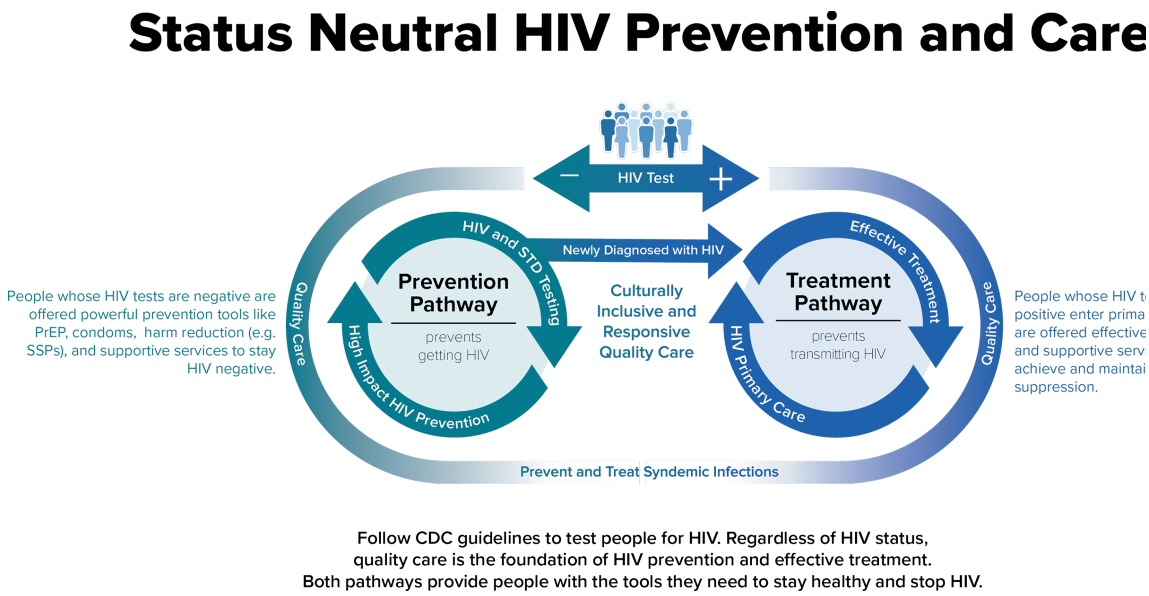

Figure 2.5.1. The status neutral approach to HIV prevention and care.

This infographic is reproduced from the US CDC (United States Centres for Disease Control and Prevention) under a Creative Commons Attribution Licence 2.0[100].

2.6. Access to PrEP in Canada

Oral PrEP was approved by Health Canada in 2016[101]. However, shortly after the IPERGAY trial ended in 2013[76], the Québec provincial government issued interim PrEP guidelines recommending use of oral TDF/FTC for those at high risk of HIV acquisition[101]. All other provinces and territories awaited Health Canada's approval and the release of Canadian guidelines before enabling PrEP access in their jurisdiction. The Québec government has continued to maintain its own PrEP guidelines, which have since indicated oral PrEP for gbMSM and transgender women that had condomless anal sex in the past six months and one of the following[101-103]:

1. Use of non-occupational PEP twice or more in their lifetime

2. Infection with syphilis or an anal bacterial sexually transmitted infection in their lifetime *(update 2019: especially if in the last 12 months)*

3. Sex with a partner living with HIV whose risk of transmission is considered high

4. Two or more sex partners in the past six months

5. Use of psychoactive substances during sex

Canada's national PrEP guidelines, released in 2017[104], set indications like that in Québec. The exception is that, rather than assess items 4. and 5. above, the high-incidence risk index (HIRI)[105] score is used, indicating PrEP for those scoring 11 or higher[104]. The HIRI score is based on an individual's age and engagement in certain behaviours in the past six months (number of male sex partners and, of those, the number living with HIV, number of condomless receptive anal sex acts, number of insertive anal sex acts with a partner living with HIV, use of poppers, and use of amphetamines)[105]. For PWID, both sets of guidelines suggest PrEP only be considered for those that report sharing injection drug paraphernalia[102-104]. The reasons for this are two-fold. Firstly, only one trial has involved PWID to date, and while showing a 49% (95%CI: 10%-72%) oral PrEP efficacy[106], the study limitations left it ranked as moderate level evidence. Secondly, there are other highly effective HIV prevention strategies available for PWID with supplemental benefits. These include needle and syringe programs (NSP) and opioid agonist therapy (OAT), which prevent the transmission of HIV and other STBBIs. OAT also provides other health benefits related to substance use disorders[102-104].

While now available country-wide, the cost of PrEP can still prohibit use for eligible gbMSM. Lower-cost generic TDF/FTC has been available in Canada since 2017[107, 108]. Nevertheless, without subsidies, the price is still approximately CAD$250/month[109]. In Québec, the provincial drug insurance program, the *Régie de l'assurance maladie du Québec* (RAMQ), has included coverage for oral PrEP (TDF/FTC) since the release of its interim guidelines in 2013. However, this drug insurance program includes a monthly co-payment of up to CAD$96.74 (as of 2023) for all medications dispensed[110]. Thus, PrEP is not necessarily cost free for all those clinically eligible in the province. In other provinces and territories, subsidies for PrEP costs began after 2017 and vary in their eligibility criteria and coverage amounts (Table 2.6.1)[111]. In fact, in Alberta, British Columbia, and Saskatchewan, as well as some subpopulations in Ontario, PrEP is provided at no cost to

the user (Table 2.6.1)[111]. In addition, the Federal Non-Insured Health Benefits (NIHB) program fully covers the cost of PrEP for registered First-Nations and Inuit peoples[111].

Table 2.6.1. Public funding of pre-exposure prophylaxis (PrEP) in 2022 across provinces and territories in Canada[107, 108, 111].

Province or territory	PrEP funding
Alberta	Full: funded for those meeting the clinical guidelines and prescribed PrEP from a designated provider
British Columbia	Full: funded for those meeting the clinical guidelines
Manitoba	Partial*
New Brunswick	Partial*
Newfoundland and Labrador	Partial*
Northwest Territories	Full
Nunavut	Full
Nova Scotia	Partial*
Ontario	1. Fully funded for those ≥24 years old or those covered by the *Ontario Works* or the *Ontario Disabilities Support Program* 2. Partial funding through the provincial drug program*
Prince Edward Island	Full: funded for those that receive approval from the chief public health office
Québec	Partial*
Saskatchewan	Full
Yukon	Full: funded for those without private insurance

*Partial funding is provided through individual provincial drug programs, which can differ in enrollment eligibility criteria and insurance plan costs.

2.7. HIV surveillance in Canada and Québec

Public health surveillance involves systematically collecting, analyzing, interpreting, and disseminating health data[112]. In Canada, public health surveillance is a responsibility shared by all levels of government. However, the provision of health care is under provincial jurisdiction. Consequently, the collection of primary surveillance data often occurs at the provincial level. Each province's surveillance system can differ in governance, structure, and data collection and dissemination processes. The passive HIV and AIDS surveillance data commonly collected across provinces include the date of diagnosis, age, sex, and HIV

exposure risk category (i.e., sex between males, both sex between males and injection drug use, injection drug use, heterosexual sex, migrating to Canada from a country where HIV is endemic, and others). Other epidemiologically relevant data measured by some provinces include race, ethnicity, time since the last negative HIV test, and CD4 cell count at diagnosis. Additionally, some provinces link their surveillance data to clinic and/or prescription data sources to capture engagement in HIV care and treatment[47].

At the federal level, PHAC works with the provincial systems to collect and analyze nationwide surveillance data. PHAC maintains a national surveillance system for HIV and AIDS that is passive and case-based, annually combining non-nominal data that the provinces and territories voluntarily provide[113, 114]. Which data is collected and submitted can vary by jurisdiction and year[113, 114]. For example, Québec historically has not submitted exposure risk category data[114]. Only in 2020 was this information provided by Québec and all other provinces[114]. Moreover, the HIV diagnosis data submitted to PHAC were stratified by new or previously diagnosed for the first time in 2020 (except for Québec)[114]. A further difference between the provincial and territorial data lies in the extent of data capture based on the reporting practices and laws governing the mandatory reporting of HIV in each jurisdiction. For example, in Québec, HIV is only mandatory to report (with nominal information) if a PLHIV has donated or received blood, blood products, organs, or tissues[115]. Altogether, variations in the different surveillance systems can hamper a clear national picture and cross-jurisdictional comparisons of Canada's HIV epidemics.

2.8. Monitoring HIV elimination with surveillance data

The purpose of HIV surveillance is to understand the epidemic and monitor trends so that public health can take effective, actionable responses to limit its transmission and reduce its burden on the population. However, case-based data only captures those diagnosed and reported to the surveillance system, which can vary not only because HIV transmission patterns change, but because patterns in other factors, such as HIV testing and migration, change. The timeliness of reporting can also affect epidemic monitoring[116]. Moreover, the data collected is typically restricted to the most direct epidemiological and clinical indicators described above. Thus, this data does not allow for directly monitoring some

essential epidemic metrics, including HIV incidence and prevalence, or uncovering the upstream epidemiological characteristics driving transmission, such as the sociodemographic and societal factors responsible for a disproportionate impact of HIV among key populations.

Active forms of HIV surveillance can help overcome the limitations of surveillance data for estimating key HIV epidemic metrics. Rather than rely on submitted reports, this involves seeking out population-based information. However, even active surveillance has significant limitations, especially in settings with concentrated HIV epidemics like Canada. For example, cohort studies aiming to measure HIV incidence among key populations in Canada can be challenged by 1) the ability to identify and obtain a representative sample of its members, 2) the large sample size needed to detect reductions and precisely measure HIV incidence[116], and 3) the loss to follow up due to the multifaceted vulnerabilities faced by members of key populations. Similar limitations can apply to cross-sectional studies[116].

Surveillance systems and analytic methods to use surveillance data to estimate key epidemic metrics are evolving[116-118]. In Canada, PHAC has developed a statistical method that uses data from the national surveillance system to estimate annual numbers of incident or new HIV acquisitions[47, 119]. The agency also works with each province and territory to understand their treatment and care cascade based on their available data and produce national estimates of UNAIDS targets[47]. Thus, HIV surveillance data remains the backbone of monitoring the HIV epidemic and progress towards elimination in Canada.

2.9. Evidence and knowledge gaps

Achieving and maintaining HIV elimination requires an actionable response based on effective, sustainable policies. However, the first step in such a response is comprehensively understanding and evaluating the epidemic –a notion framed by UNAIDS as "*know your epidemic, know your response*"[96, 120]. Critical evidence on this front is needed to inform the forthcoming HIV response in Québec. Firstly, a detailed analysis of combination HIV prevention among Montréal gbMSM that captures antiretroviral-based strategies is needed. Such an analysis will renew the city's understanding of what HIV prevention strategies are in use and by whom and allow for identifying possible gaps in the

reach of current prevention programs. Secondly, a thorough understanding of the role of past programs and policies on current HIV dynamics is needed to conceptualize the path forward and prioritize actions. To this end, an evaluation of PrEP use on the HIV epidemic among Montréal gbMSM is needed. Finally, the dynamic nature of prevention and other epidemic drivers necessitate monitoring trends in new HIV acquisitions. Therefore, reporting on HIV incidence by key population can more accurately identify progress towards elimination, compared to only monitoring new diagnoses through surveillance data, and can highlight where further efforts might be needed.

Chapter 3. Methods Overview

3.1. Data sources

This thesis leverages several data sources to achieve my research objectives, from population-based and clinical cohorts, to repeated cross-sectional surveys and surveillance data. This chapter describes the main surveys and data sources used and provides an overview of the chosen methodological approaches. These data are important to parameterize, calibrate, and validate the mathematical models used in objectives 2 and 3 of this thesis.

3.1.1. SurvUDI

PHAC and provincial public health authorities often undertake enhanced HIV surveillance, including the *M-Track* and *I-Track* surveys to monitor HIV and other STBBIs among gbMSM and PWID, respectively. In Québec, the long-standing *SurvUDI* surveillance network contributes to *I-Track*. Since 1995, the *SurvUDI* network has performed annual surveillance of PWID across Québec and in Ottawa, Ontario[121, 122]. Each year, a cross-sectional survey is conducted among people aged 14 years and older that injected drugs in the past six months (referred to in this thesis as active PWID). Participant recruitment occurs at sites where PWID are commonly encountered, including needle exchange sites, rehabilitation and detention centres, and shelters[122]. Over time, more than 15,000 active PWID have participated in *SurvUDI*[122]. Using an interviewer-administered questionnaire, the survey collects self-reported information on participant socio-demographic characteristics, drug use and sexual behaviours, and history of HIV and hepatitis C virus (HCV) testing and care[122]. Testing for HIV and HCV is also performed on participant saliva samples[122]. This thesis used *SurvUDI* data in objective 3 to inform the age distribution of injection drug initiation.

3.1.2. Argus

As part of *M-track*, the Montréal public health department and INSPQ collaborated with PHAC to establish *Argus*, a two-wave cross-sectional study of gbMSM[123-125]. The waves

took place in Montréal over 2005-2007 (*Argus I*) and in Montréal, Laval, and Québec City over 2008-2009 (*Argus II*) and recruited 1,957 and 1,873 participants, respectively[123-125]. A modified time-location sampling method was used to recruit participants at various locations where gbMSM were known to socialize, including bars, saunas, and sports and recreation facilities[123-125]. The men approached could participate if they were at least 18 years of age, had sex with a man (ever), and could read in French or English[123-125]. Those recruited at a venue in Montréal additionally had to be a resident of the island of Montréal.

With a self-administered paper questionnaire, *Argus* collected data on various sociodemographic and sexual health and behavioural factors. Dry blood spot samples were also taken to test for HIV and other STBBIs. In objective 3 of this thesis, HIV prevalence and self-reported ART coverage were estimated from *Argus* and used as cross-validation data. In addition to these variables, sexual behavioural and intervention use data from *Argus* were used to develop the model used in objective 2 (i.e., the number and type of sexual partnerships, mixing patterns, and use of condoms, HIV testing, PEP, and ART).

3.1.3. Engage Cohort

Funded in 2015, *Engage* began in 2017 as a two-wave cross-sectional study of sexually active Canadian gbMSM residing in Montréal, Toronto, and Vancouver, with the second wave capturing the same study sample one year later. The Engage study was further extended to a cohort (2019-2023). The primary study aim was to estimate the prevalence and incidence of HIV and other STBBIs within these populations and their sexual health and STBBI prevention needs[126]. At each site, respondent-driven sampling (RDS) was used to recruit participants[127]. RDS is a variation of chain referral sampling leveraging social networks to obtain samples representative of hidden populations[128]. In Montréal, the final sample was composed of 1,179 gbMSM aged 16 years or older that identified as a man, had sex with another man in the past six months, and could read in French or English[126, 127].

Guided by a sexual health framework[129], a computer-assisted questionnaire capturing a variety of determinants of sexual health outcomes was completed by all *Engage* participants. Participants also attended an appointment with a nurse where blood samples

were taken to test for HIV and other STBBIs. *Engage* data was used in all three of my thesis objectives as a rich data source with recent bio-behavioural data collected from gbMSM in Montréal. The baseline data was available early on, enabling me to assess the use of PrEP and other HIV prevention strategies at that time (objective 1). The subsequent study extension was key to my second and third objectives, providing longitudinal data that informed a variety of model parameters and stood as valid calibration and cross-validation outcomes, including HIV incidence and PrEP uptake measures.

3.1.4. L'Actuel PrEP Cohort

For nearly 40 years, Montréal's *Clinique médicale l'Actuel*, located in the city's Gay Village, has remained an important, community-based sexual health clinic and a main site for HIV and STBBI testing and treatment referrals for the city's gbMSM[130]. In addition to care provision, *l'Actuel* also undertakes clinical research. In preparation for PrEP approvals in Canada, *l'Actuel* supported a survey exploring interest in PrEP among gbMSM attending its rapid HIV testing site (*Actuel sur Rue*)[131]. The survey indicated that if PrEP proved effective for HIV prevention, 55% of the participants would be interested in taking it[131]. Thus, to provide PrEP services *l'Actuel* opened the first PrEP clinic in Canada in 2013 (following Québec's interim PrEP guidelines) and concomitantly established *l'Actuel PrEP Cohort* to assess the real-world, individual-level effectiveness of PrEP and usage characteristics in Montréal[130].

Recruitment into *l'Actuel PrEP Cohort* is ongoing, with those 18 years or older consulting for and prescribed PrEP at the clinic routinely invited to participate. The medical and research staff on-site obtain clinical, sociodemographic, and behavioural data at each consult and follow-up visit (one month after the first PrEP prescription and every subsequent three months) for as long as the participant continues to receive services at the clinic. An analysis of the cohort data collected up to 2018 noted that 97% of the 2,156 participants were gbMSM. This clinical cohort helped characterize the characteristics of PrEP users in objective 2 of my thesis[130].

3.1.5. Public health data on new HIV diagnoses in Québec

AIDS cases were under surveillance in Québec from 1979-2002. I abstracted the number of AIDS cases reported over that period from provincial reports[132, 133]. Data on all new HIV diagnoses from 2002 to 2020 was requested from the *Institute de santé publique du Québec* (INSPQ). The database contains aggregated information on the annual number of new diagnoses by age groups, risk exposure category, the self-reported time since the last negative HIV test result, CD4 cell count at diagnosis (from 2013 onward), and region (*Région sociosanitaire 06*, corresponding to Montréal, and the whole province). This database is comprehensive and covers the whole population of Québec with a *numéro d'assurance maladie* (NAM). Diagnoses without NAM became reportable to the INSPQ in 2012. Altogether, the INSPQ surveillance data constituted a crucial data source for my thesis, with the mathematical models developed in objectives 2 and 3 being calibrated and cross-validated to this data.

3.2. Mathematical models for infectious disease transmission

Inference about infectious disease transmission can be challenging, with incidence often unobservable, HIV testing patterns affecting measures obtained from passive surveillance methods, and multiple causal factors related to transmission that can be difficult to capture. It is important to monitor changes in HIV acquisitions over time, but empirical methods face several challenges. For example, cohort studies need a large sample size to obtain precise estimates and loss to follow-up can bias findings. Similarly, cross-sectional studies that use an HIV recency assay to detect recent HIV acquisitions would need a prohibitively large sample size in low incidence settings such as Montréal. In such instances, mathematical models that leverage routine surveillance data offer a suitable alternative to monitor incidence (objective 2). Further, transmission dynamics models can help assess the impact of past interventions (objective 3). Mathematical models are computer simulations of epidemics that represent the transmission of a pathogen through a set of mathematical equations (or rules) that enables researchers to "translate" the impact of the diseases clinical course at the individual level, assess its distribution in the population, and to explore a wide range of "what if" scenarios[134]. The model's mathematical structure

simplifies the complex underlying transmission phenomenon. In doing so, a mathematical model can overcome the aforementioned challenges by explicitly mapping the factors affecting transmission and simulating incidence.

Two types of models are used in this thesis: phenomenological and mechanistic models. The former, including statistical prediction models and certain mathematical models, are interested in parameter estimation without explicitly modeling the transmission mechanism[135]. Mechanistic models, on the other hand, aim to understand causal relationships and thereby explicitly simulate the dynamics of infectious disease transmission with a force of infection depending on the prevalence of unsuppressed viral load, contact patterns and sexual mixing, and other essential infection determinants (e.g., PrEP, PEP, condom use)[134].

Mechanistic mathematical models can be compartmental or agent-based (ABM). Compartmental models describe what happens on average in the population, grouping individuals into compartments based on disease status and other factors important to transmission, including sex, age, and intervention use[135]. In developing a compartmental model, a system of equations that describe the number of individuals transitioning in and out of each compartment are evaluated over time[135]. The system of equations, typically ordinary differential equations, is then solved numerically using methods such as the Euler and 4th-order Runge-Kutta methods. Instead of tracking groups of individuals, agent- or individual-based models track each individual in the population and incorporate the effect of chance into the disease spread[135, 136]. Because of this stochasticity, agent-based models are repeatedly simulated, and the distribution of results is summarized[135].

In objective 2 of this thesis, a mechanistic ABM is used to evaluate the impact of PrEP intervention among Montréal gbMSM. While ABMs can be more computationally expensive, this is less concerning when the number of compartments is increasingly large. Considering HIV transmission in Montréal gbMSM, there are many stratifications necessary to model. These include disease status (including diagnosis and treatment stratifications), age, sexual activity level, sexual position preference (i.e., insertive, receptive, or versatile), and intervention use (i.e., condoms, PEP, PrEP, and ART with viral

suppression). Thus, an ABM was used as a more straightforward method to track all such elements.

In contrast, the model developed in objective 3 is a phenomenological, deterministic compartmental model that estimates HIV incidence parameters using Bayesian back-calculation methods. This type of model is more appropriate for this objective compared to an ABM because it requires less information to estimate the unobserved outcome of interest (HIV incidence) using routine surveillance data (new HIV diagnoses)[137]. Back-calculation methods are those that make inference on an initiating event based on observed occurrences of subsequent events[138]. For this objective, I developed a back-calculation model to estimate the incidence of HIV using the subsequent events of HIV diagnosis, AIDS diagnosis, or HIV/AIDS-related death. As a phenomenological model, individuals are assumed to become infected at a time-dependent (and, when possible, age-dependent) rate estimated by calibrating the model to routinely collected data.

3.3. Ethics

This thesis leveraged existing data to perform secondary data analysis. All data obtained was anonymized and de-identified and used only as authorized for these research projects. Ethics approvals were obtained from the *Research Institute of the McGill University Health Centre* (Objective 1) and the *McGill Research Ethics Board* (Objectives 2 and 3).

Chapter 4. Manuscript 1: Combination HIV prevention strategies among Montréal gbMSM in the PrEP era: a latent class analysis

4.1. Preface to Manuscript 1

In alignment with "*knowing your epidemic, knowing your response,"* the first two priority actions of the *HIV Prevention 2025 Road Map* are to 1) assess HIV programs' needs and barriers and 2) adopt an HIV precision prevention approach to reach elimination goals[3]. For Montréal, knowing how gbMSM in the city currently use HIV prevention will help calibrate and re-focus the response. A study by Otis et al. established a picture of HIV prevention in this population in the early 2010s[139], just before PrEP became available and ART treatment guidelines expanded access to all PLHIV and "undetectable = untransmissible" messaging began. Considering these additions to the available set of HIV prevention strategies, I updated our understanding of combination HIV prevention patterns among Montréal gbMSM using the only RDS (i.e., improved representativeness) sample of gbMSM to date. I also assessed characteristics associated with the identified patterns of prevention practices to contextualize the findings by indicating who is using what. The resulting article was published in *AIDS and Behavior* in January 2021[127].

4.2. Manuscript 1: Combination HIV prevention strategies among Montréal gay, bisexual, and other men who have sex with men in the PrEP era: a latent class analysis

Carla M. Doyle[1], Mathieu Maheu-Giroux[1], Gilles Lambert[2], Sharmistha Mishra[3,4,5], Herak Apelian[2], Marc Messier-Peet[2], Joanne Otis[6], Daniel Grace[7], Trevor A. Hart[8,9], David M. Moore[10,11], Nathan J. Lachowsky[12], Joseph Cox[1,2,13] and the Engage Study Team

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, QC

[2]Direction Régionale de Santé Publique de Montréal, Montréal, QC

[3]Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON

[4]Institute of Medical Sciences, University of Toronto, Toronto, ON

[5]Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[6]Département de Sexologie, Université du Québec à Montréal, Montréal, QC

[7]Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[8]Department of Psychology, Ryerson University, Toronto, ON

[9]Division of Social & Behavioural Sciences, Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[10]BC Centre for Excellence in HIV/AIDS, Vancouver, BC

[11]Faculty of Medicine, University of British Columbia, Vancouver, BC

[12]School of Public Health and Social Policy, University of Victoria, Victoria, BC

[13]Clinical Outcomes Research and Evaluation, Research Institute - McGill University Health Centre, Montréal, QC

Corresponding Author: Dr. Joseph Cox

Address for Correspondence: joseph.cox@mcgill.ca

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Key Words: combination HIV prevention, HIV prevention strategies, men who have sex with men, pre-exposure prophylaxis, latent class analysis

ABSTRACT

Pre-exposure prophylaxis (PrEP) became publicly available in Québec for gay, bisexual and other men who have sex with men (GBM) in 2013. We used baseline data from Engage, a cohort of GBM recruited by respondent-driven sampling, to examine patterns of combination HIV prevention use among Montréal GBM since PrEP became available. Latent class analysis, stratified by HIV status, was used to categorize GBM by self-reported use of biomedical and behavioral prevention strategies. Correlates of resulting classes were identified using multinomial logistic regression. Among HIV-negative/unknown GBM (n=968), we identified four classes: *low use of prevention* (32%), *condoms* (40%), *seroadaptive behavior* (21%), and *biomedical* (including PrEP; 7%). Those using prevention (*condoms*, *seroadaptive behavior*, and *biomedical*) had a higher number of anal sex partners and were more likely to report a recent sexually transmitted infection diagnosis. GBM using biomedical prevention also had a higher level of formal education. Among GBM living with HIV (n=200), we identified three classes: *mainly antiretroviral treatment (ART) with viral suppression* (53%), *ART with viral suppression and condoms* (19%), and *ART with viral suppression and seroadaptive behavior* (18%). Again, the number of anal sex partners was higher among those using condoms and seroadaptive behaviors. Our findings show antiretroviral-based prevention, either alone or in combination with other strategies, is clearly a component of the HIV prevention landscape for GBM in Montréal. Nevertheless, PrEP uptake remains low, and there is a need to promote its availability more widely.

Introduction

Gay, bisexual, queer, and other men who have sex with men (GBM), including transmen, bear a disproportionate burden of HIV in Canada (1). The most recent national estimate suggests GBM accounted for 41% of diagnosed HIV infections in 2018 (1). In the province of Québec, which had the second-largest proportion of HIV diagnoses in the country (1), GBM comprised 58% of those occurring in males, and the majority were in the Montréal metropolitan area (2). In 2017, Montréal announced it would become the first UNAIDS Fast-Track city in Canada (3) and committed to ending the HIV/AIDS epidemic by 2030 (4). With this renewed drive towards HIV elimination, it is necessary to assess current strategies used for HIV prevention by GBM in Montréal and to understand the factors associated with prevention use to devise appropriate prevention policy and programming.

Combination HIV prevention hinges upon the concurrent use of behavioral, biomedical, and structural prevention strategies to reduce HIV transmission (5). By promoting a targeted set of prevention strategies working synergistically on multiple levels (e.g. individual, partnership, and population), combination prevention programs can have an improved impact on transmission (6, 7). At the individual level, combination prevention can involve simultaneously practicing more than one strategy, or adopting one during a specific time or context, while adopting alternative strategies in others. Early in the epidemic, the conventional biomedical HIV prevention strategy promoted for GBM was condom use during anal sex (8-10). However, GBM have come to use and combine additional strategies over time to prevent the acquisition and transmission of HIV. These include behavioral seroadaptive strategies, such as serosorting and strategic positioning (11-17), and other biomedical prevention strategies such as HIV testing, antiretroviral treatment (ART) (18-21), post-exposure prophylaxis (PEP) (22, 23), and pre-exposure prophylaxis (PrEP) (24, 25).

The greatest potential for HIV elimination (26) lies in the use of antiretroviral medications for prevention through ART (a combination of antiretrovirals for treatment among people living with HIV) and PrEP (antiretrovirals for people uninfected with HIV). ART decreases HIV viral load to undetectable levels. Studies have shown that those on ART with an undetectable viral load do not transmit the virus to their sexual partners (18-21), giving rise

to the notion of Undetectable=Untransmissible (U=U) (27) and ART as prevention. PrEP is also highly effective in preventing HIV acquisition (24, 25). The evolution of these two strategies has led to the HIV "status-neutral" approach to prevention programming, which emphasizes the engagement of individuals into clinical HIV care, regardless of HIV status (28). In this way, both people living with HIV and HIV-negative individuals similarly enter a cascade of care, be-it for treatment or prevention. Such an approach is now fundamental to combination HIV prevention, with U=U and PrEP especially being prioritized by elimination efforts (29-31).

Previous Canadian studies have examined the use of prevention strategies among GBM (32, 33), but did not always include GBM living with HIV (32). Further, these were conducted before PrEP became formally recommended. In 2013, Québec became the first Canadian province to publicly reimburse antiretroviral medication (Truvada) for PrEP for at-risk GBM (34); it remained the only one to do so until 2017 when other provinces followed. Consequently, combination HIV prevention including the use of PrEP-related strategies has yet to be understood in Québec and elsewhere in Canada.

Latent class analysis (LCA) is a statistical method that identifies underlying patterns in data to uncover groupings (latent classes) of individuals that are similar according to particular characteristics (35, 36). Many studies have used this method to understand various characteristics and behaviors related to HIV, including sociodemographic and sexual risk practices (37), substance use (38-40) and other syndemic factors (41), as well as prevention use among GBM in Canada (32, 33) and elsewhere (42, 43). Given the number of existing strategies, LCA can be useful for discerning relevant patterns in prevention use. Rather than using pre-determined categories that may not meaningfully describe the reality, LCA considers all potential combinations of strategies and simplifies this complexity by identifying the most frequently occurring response patterns in the data (35, 36). For a full picture, we can further determine the attributes of individuals within each class to explain who utilizes particular types of prevention. Factors previously found to be associated with prevention use range across many dimensions, such as sociodemographic (including social support (44, 45)), sexual health (including sexual behaviors, relationships, attitudes, and sexually transmitted or blood-borne infections

[STBBIs] (32, 46)), substance use, and other health-related factors (including mental health (44, 47, 48)).

We aimed to describe the prevention strategies currently practiced by GBM in Montréal, the second-largest Canadian city and epicenter of the HIV epidemic in Québec. Our objectives were to 1) examine patterns in the use of prevention strategies among HIV-negative GBM and GBM living with HIV in Montréal distinctively and 2) describe the potentially important sociodemographic, behavioral and health-related factors associated with observed patterns. This assessment could aid policymakers in identifying prevention gaps and inform future responses to ensure prevention uptake is in-line with elimination needs.

Methods

Study Population

Engage is a prospective cohort study of GBM in Montréal, Toronto, and Vancouver. We included the baseline data of participants from Montréal (46), where recruitment occurred between February 2017–June 2018. Cisgender and transgender men aged ≥16 years were eligible to participate if they had sex with another man in the past six months (P6M), resided in the greater Montréal area, could read in French or English and consented to participate. All participants completed a computer-assisted questionnaire in French or English and underwent HIV and other STBBI testing with a study nurse.

Participants were recruited using respondent-driven sampling (RDS) (49). Initial participants were purposively selected to initiate recruitment chains, with successive participants distributing up to six coupons to recruit peers. Participants were compensated $50 for their initial enrollment and $15 for each successful recruit. RDS results are presented following STROBE-RDS guidelines (50); see Appendix I.

Ethics approval for the Montréal Engage site was obtained from the Research Institute of the McGill University Health Centre.

Use of HIV prevention strategies by HIV status

Self-reported HIV status, defined by the self-reported result (in the questionnaire and to the nurse) of their last HIV test, was used as this captured each participant's awareness of their serostatus at enrollment, and this would have influenced prior sexual behaviors and prevention use. Those who reported never tested, unsure if ever tested, or never receiving their last result were considered not to know their HIV status and were assumed to have similar sexual behaviors to HIV-negative men. Thus, we dichotomized HIV status to HIV-negative/unknown and HIV-positive (33, 51, 52). Those that self-reported as HIV-negative/unknown in the questionnaire but as living with HIV to the study nurse were considered HIV-positive (n=11) and excluded from these analyses, as the questionnaire's skip pattern resulted in missing information on the prevention strategies for people living with HIV. As the use of HIV prevention differs according to HIV serostatus, we considered two sets of strategies: 1) those among HIV-negative/unknown and 2) those among individuals living with HIV. Within each, we included biomedical (testing, condom and antiretroviral-based) and behavioral (seroadaptive) prevention strategies, as these are most proximal to HIV acquisition and transmission (53). All measures of prevention were self-reported (see Appendix II for survey questions).

HIV-negative/unknown individuals

Measures concerning prevention of HIV acquisition among HIV-negative/unknown GBM included: recent HIV testing (P6M); consistent condom use (*always used condoms for anal sex*; P6M); any PEP use (ever); any PrEP use (P6M); any strategic positioning (*positioned as the top [insertive partner] for anal sex to prevent acquiring HIV*; P6M); any serosorting (*condomless sex with known HIV-negative men to prevent acquiring HIV*; P6M); and any viral load sorting (*condomless sex with HIV-positive men who have an undetectable viral load*; P6M).

Individuals living with HIV

Measures concerning prevention of HIV transmission by GBM living with HIV included: consistent condom use (as above; P6M); ART with viral suppression (self-reported undetectable viral load [<50 copies/mL]; current); any strategic positioning *(positioned as the bottom [receptive partner] for anal sex to prevent transmitting HIV*; P6M); any

serosorting (*condomless sex with known HIV-positive men to prevent transmitting HIV*; P6M); any PrEP-use sorting (*condomless sex with HIV-negative men using PrEP*; P6M).

Statistical Analyses

We described sample characteristics with and without RDS-adjustment.

Latent Class Analyses

We used LCA to empirically categorize participants into classes based on their use of prevention strategies. All LCA models were stratified by self-reported HIV status and included corresponding indicators for the use of prevention strategies (defined above).

An assumption of LCA is conditional independence (35, 54). Among the HIV-negative/unknown prevention strategies, by definition, separate indicators for serosorting and viral load sorting would likely be conditionally dependent, as would separate indicators for serosorting and PrEP-use sorting among the HIV-positive prevention strategies. To relax the assumption of conditional independence, a single item for serosorting or viral load sorting (yes to either vs. no to both) was used in the HIV-negative/unknown LCA models, resulting in a measure of having any condomless sex with GBM that could reduce the risk of HIV acquisition as a seroadaptive strategy. In the HIV-positive models, a four-level joint item indicator (55) for serosorting and/or PrEP-use sorting was used (using both, PrEP-use sorting and not serosorting, serosorting and not PrEP-use sorting, and neither). Conditional dependence might also arise if participants responded consistently to the survey items for condom use, serosorting, viral load sorting, and PrEP-use sorting (Appendix II). To assess the validity of the conditional independence assumption, we examined the bivariate residuals between pairs of strategies (56). Aside from the abovementioned exception of serosorting and/or PrEP-use sorting, binary indicators were used in the LCA models.

The optimal number of latent classes was based on the interpretability of those classes and model fit criterion; mainly Bayes Information Criterion (BIC), Akaike Information Criterion (AIC), and entropy (57). Specifically, models with 1-5 classes and 1-3 classes were investigated for the HIV-negative/unknown and the HIV-positive models, respectively. Class profiles were assessed based on the resulting conditional probabilities

and labels were assigned qualitatively according to the main and defining strategies used. Class sizes were adjusted using the RDS-II-estimator (58), which applies inverse probability of sampling weights proportional to participant network size.

Correlates of class membership

Factors known (32, 33, 44, 45, 59-61) or hypothesized to be associated with use of prevention strategies that were well-measured, had few missing data (<5%), and had sufficient cell counts (≥5) when stratified by class (HIV-positive models), were selected a priori and included as covariates in multivariable regression models. Sociodemographic factors were: age, sexual orientation, ethnicity, education and social time spent with gay/bisexual guys. Sexual health and related factors included: unknown HIV status (HIV-negative models), STBBI diagnosis in the past 12 months (P12M), number of anal sex partners (P6M), HIV status of main partner (HIV-negative models; we used having a main partner in HIV-positive models due to small cell counts), perceived risk of acquiring/transmitting HIV, and HIV treatment optimism (measured by the HIV Treatment Optimism-Skepticism Scale (62), which ranges from 0-36, with higher scores indicating higher optimism in ART). Other health-related factors included: having a regular health care provider and perceived mental health (P6M). Finally, substance use factors included: use of crack or cocaine (P6M), use of other drugs, and alcohol misuse (measured by the Alcohol Use Disorders Identification Test, consumption questions [AUDIT-C] (63), which ranges from 0-12, where higher scores indicate higher risk of alcohol affecting one's health and safety; scores were dichotomized at 4, the optimal cut point for identifying alcohol dependence in men (64)).

Multinomial Logistic Regression Modeling

Univariable and multivariable multinomial logistic regression models stratified by self-reported HIV status assessed the factors associated with each class. Class membership was assigned by modal assignment, according to the class each individual had the highest probability of belonging to. The referent class was chosen based on size and consistency between the HIV-negative/unknown and HIV-positive models. As there was very little missing data among the factors modelled (≤3.1%), complete case analyses were performed. RDS weights were not included, as these may be unwarranted in regression modeling (65).

Robust standard errors were used to account for clustering by each recruiter within the referral chain.

All analyses were conducted in the R statistical software using the *poLCA*, *mlogit*, and *sandwich* packages (66-68).

Results

Study Population

Engage enrolled 1168 participants in Montréal: 200 (17%) self-reported as living with HIV and 863 (74%) as HIV-negative; the remaining 105 (9%) did not know their HIV status (total of 968 HIV-negative/unknown participants).

Table 4.2.1 summarizes the participant sociodemographic characteristics. The mean age of participants was 38 years (standard deviation (SD): 14). The majority identified as a man (94%) and as gay (86%). Approximately half of the sample identified as French Canadian, 65% had a post-high school diploma or higher, and 43% had an annual income of CAD 30,000 or more. Over half (57%) did not have a main partner at the time of participation. The mean number of anal sex partners (P6M) was 7 (SD: 15), and 31% of participants reported an STBBI diagnosis (P12M).

Table 4.2.1. Unadjusted and RDS-II adjusted estimates of socio-demographic characteristics of the Engage-Montréal study participants, 2017–2018 (n=1168)[a]

Characteristic	Overall (n=1168)		HIV-negative/ unknown (n=968)		HIV-positive (n=200)	
	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)
Age (mean)	38 (SD: 14)	38 (36-39)	36 (SD: 13)	36 (35-37)	49 (SD: 11)	50 (48-52)
Gender: identify as a man[b]	1101 (94%)	92% (89%-95%)	912 (94%)	92% (88%-95%)	189 (95%)	93% (89%-98%)
Sexual orientation: Gay[c]	1009 (86%)	81% (77%-85%)	827 (85%)	80% (75%-84%)	182 (91%)	90% (81%-98%)

Characteristic	Overall (n=1168)		HIV-negative/ unknown (n=968)		HIV-positive (n=200)	
	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)
Ethnicity:						
French Canadian	605 (52%)	44% (39%-49%)	477 (50%)	43% (37%-48%)	128 (66%)	57% (45%-69%)
English Canadian	111 (10%)	10% (7%-13%)	89 (9%)	9% (6%-12%)	22 (11%)	17% (7%-26%)
European	156 (14%)	15% (11%-18%)	142 (15%)	16% (12%-19%)	14 (7%)	8% (1%-14%)
Other	283 (25%)	31% (26%-36%)	253 (26%)	33% (27%-38%)	30 (16%)	18% (10%-27%)
Education: post-high school diploma or higher	757 (65%)	58% (53%-63%)	663 (69%)	60% (55%-65%)	94 (47%)	42% (30%-53%)
Annual income: ≥CAD$30,000	500 (43%)	33% (29%-38%)	435 (45%)	34% (29%-38%)	65 (33%)	32% (21%-43%)
Social time spent with gay/bi guys: 50% or more	521 (46%)	33% (28%-38%)	432 (46%)	32% (27%-37%)	89 (46%)	38% (27%-48%)
HIV status: unknown	105 (9%)	13% (10%-16%)	105 (11%)	15% (11%-18%)	-	-
STBBI diagnosis in the past 12 months	359 (31%)	26% (21%-31%)	255 (26%)	23% (18%-28%)	104 (52%)	44% (32%-56%)
Mean number of anal sex partners in the past 6 months	7 (SD: 15)	5 (3-7)	7 (SD: 15)	5 (3-7)	10 (SD: 16)	6 (4-8)

Characteristic	Overall (n=1168)		HIV-negative/ unknown (n=968)		HIV-positive (n=200)	
	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)
HIV status of main partner:						
No main partner	662 (57%)	56% (51%-61%)	538 (56%)	56% (50%-61%)	124 (62%)	56% (44%-68%)
Unknown/uncertain	121 (10%)	12% (8%-15%)	113 (12%)	12% (9%-16%)	8 (4%)	6% (0%-15%)
HIV-negative	328 (28%)	28% (23%-32%)	287 (30%)	29% (24%-34%)	41 (21%)	22% (12%-32%)
HIV-positive	57 (5%)	5% (3%-7%)	30 (3%)	3% (1%-5%)	27 (14%)	16% (9%-24%)
Perceived risk of acquiring/ transmitting HIV	187 (17%)	19% (15%-23%)	171 (18%)	20% (16%-25%)	16 (9%)	8% (2%-15%)
HIV Optimism-Skepticism Scale[d] (mean)	17 (SD: 6)	16 (16-17)	16 (SD: 5)	16 (15-17)	20 (SD: 6)	20 (18-22)
Currently have a health care provider	786 (67%)	60% (55%-65%)	599 (62%)	54% (49%-60%)	187 (94%)	95% (90%-100%)
Perceived mental health in the past 6 months:						
Excellent/very good	552 (49%)	47% (42%-53%)	459 (48%)	46% (40%-52%)	93 (48%)	56% (44%-68%)
Good	332 (29%)	28% (24%-33%)	278 (29%)	30% (24%-35%)	54 (28%)	19% (10%-28%)
Fair/poor	258 (23%)	24% (20%-29%)	211 (22%)	24% (19%-29%)	47 (24%)	25% (14%-37%)

Characteristic	Overall (n=1168)		HIV-negative/ unknown (n=968)		HIV-positive (n=200)	
	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)	N (%)	RDS-II % (95%CI)
Drug use: crack or cocaine in the past 6 months	318 (27%)	24% (20%-29%)	269 (28%)	24% (20%-28%)	49 (25%)	28% (18%-39%)
Drug use: other drugs in the past 6 months[e]	538 (46%)	36% (32%-41%)	429 (44%)	35% (30%-40%)	109 (56%)	43% (31%-54%)
Alcohol misuse: AUDIT-C ≥ 4[f]	685 (60%)	55% (50%-60%)	605 (63%)	57% (51%-62%)	90 (46%)	42% (30%-53%)

Abbreviations: Respondent driven sampling (RDS); confidence interval (CI); standard deviation (SD); sexually transmitted or blood borne infection (STBBI); Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C).

[a]RDS-II weights are inverse probability of sampling weights that are proportional to participant network size.

[b] Gender was defined as man versus other. The other terms used to describe one's gender included: transman, gender queer/gender non-conforming, and two-spirit.

[c]Sexual orientation was defined as gay versus other. The other terms used to describe one's sexual orientation included: bisexual, straight, queer, questioning, asexual, pansexual and two-spirit.

[d]The HIV Treatment Optimism-Skepticism Scale (62) includes items related to the efficacy of antiretrovirals for both HIV treatment and reduced infectiousness. The scale ranges from 0-36, where higher scores indicate higher optimism in antiretroviral treatment. Scores were dichotomized at the optimal cut point for identifying alcohol dependence in men (64): ≥4 vs. lower.

[e]Other drugs included any of ecstasy, crystal methamphetamine, mephedrone, speed, poppers, gamma hydroxybutyrate (GHB), lysergic acid diethylamide (LSD), and ketamine.

[f]Alcohol misuse was measured by the Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C), a screening tool for alcohol abuse, dependence, or heavy drinking (63). The AUDIT-C Scale ranges from 0-12, where higher scores indicate higher risk of alcohol affecting one's health and safety.

Latent Class Analysis: HIV-negative/unknown

Among the HIV-negative/unknown participants, a four-class model was selected based on fit statistics (Table 4.2.2) and model interpretability. None of the bivariate residuals (Table 4.2.3) violated the conditional independence assumption. The results are displayed in Figure 4.2.1; Table 4.2.2 contains the exact item response probabilities (RDS-weighted class sizes are presented in both; Table 4.3.4 provides unweighted estimates).

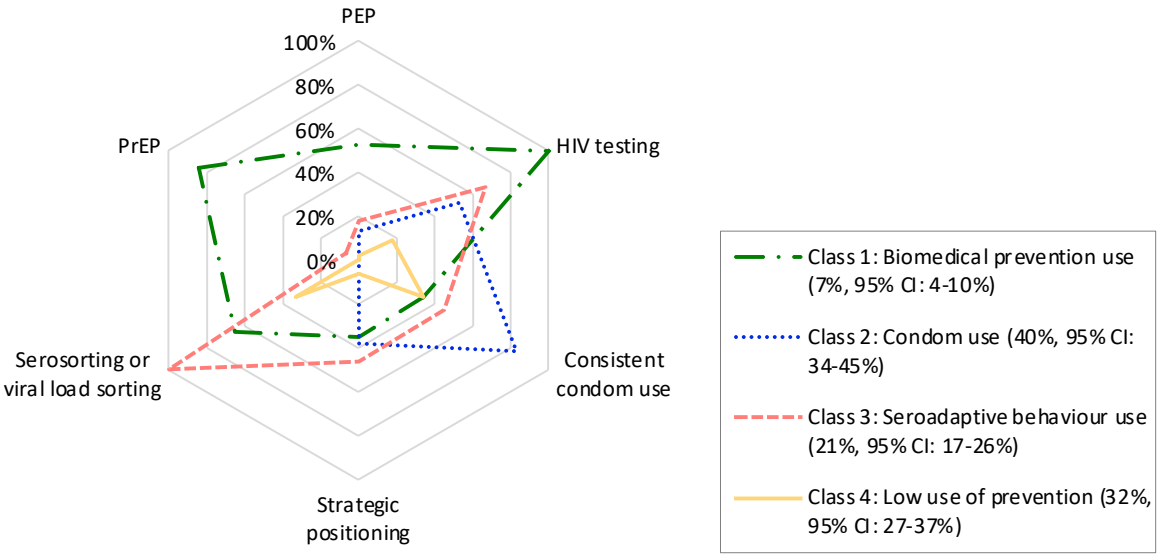
Table 4.2.2. Estimated item response probabilities of self-reported use of HIV prevention strategies among the HIV-negative/unknown participants of the Engage-Montréal study, 2017–2018 (n=968): 4 class model[a]

Variable	Class 1: Biomedical prevention use n=113 (7%, 95%CI: 4%-10%)	Class 2: Condom use n=341 (40%, 95%CI: 34%-45%)	Class 3: Seroadaptive behavior use n=241 (21%, 95%CI: 17%-26%)	Class 4: Low use of prevention n=273 (32%, 95%CI: 27%-37%)
HIV testing	100%	53%	67%	18%
PrEP	84%	0%	7%	0%
PEP	53%	13%	18%	2%
Consistent condom use	34%	83%	45%	34%
Strategic positioning	35%	38%	46%	6%
Serosorting or viral load sorting	65%	0%	100%	33%

Abbreviations: Confidence interval (CI); pre-exposure prophylaxis (PrEP); post-exposure prophylaxis (PEP).

[a]RDS-II adjusted class sizes (%) and 95% confidence intervals are presented. RDS-II weights are inverse probability of sampling weights that are proportional to participant network size.

A



B

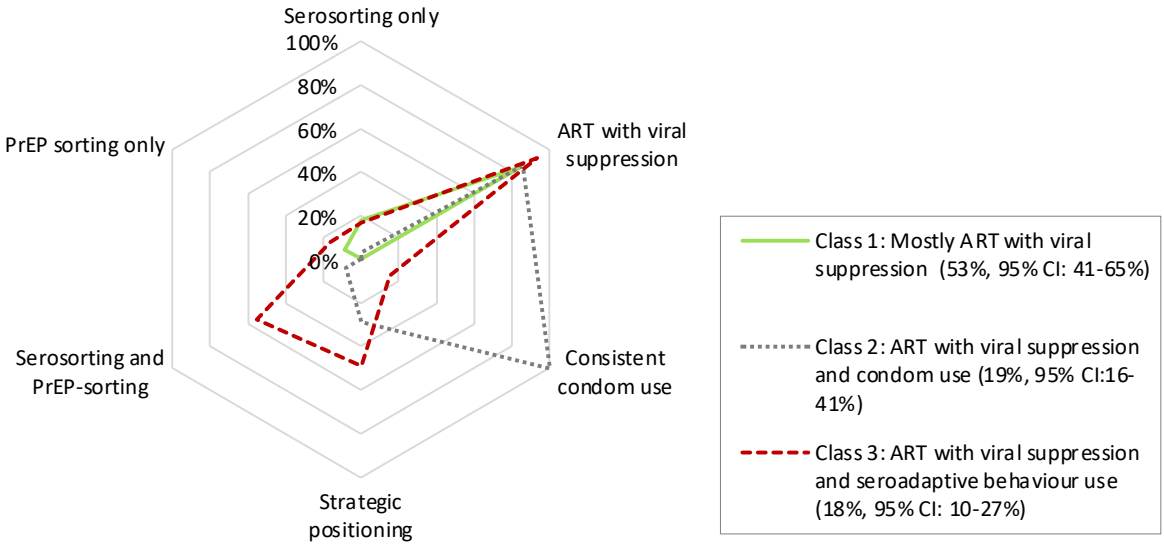


Figure 4.2.1. A) Spider plot of estimated item response probabilities of self-reported use of HIV prevention strategies among the HIV-negative/unknown participants of the Engage-Montréal study, 2017 – 2018 (n=968): 4 class model. B) Spider plot of estimated item response probabilities of self-reported use of HIV prevention strategies among the HIV-positive participants of the Engage-Montréal study, 2017 – 2018 (n=200): 3 class model.

Class 1 was labelled as *biomedical prevention use* (n=113), Class 2 as *condom use* (n=341), Class 3 as *seroadaptive behavior use* (n=241), and Class 4 as *low use of prevention* (n=273). Those in *biomedical prevention use*, the smallest class, had the highest probability of recent PrEP use (84% in P6M), ever using PEP (53%), and recent HIV testing (100% in P6M); these participants also engaged in serosorting or viral load sorting (65%). *Condom use,* the largest class, consisted of participants with high levels of consistent condom use (83%) and recent HIV testing (53% in P6M). Those in the *seroadaptive behavior use* class engaged in serosorting or viral load sorting (100%), had a recent HIV test (67% in P6M), reported consistent condom use (45%), and strategic positioning (46%). Lastly, among the *low use of prevention* class, the highest probability of using any one method corresponded to condom use (34%), followed by having performed serosorting or viral load sorting (33%); the remaining prevention strategies assessed had low probabilities.

Latent Class Analysis: HIV-positive

Among the participants living with HIV, a three-class model was selected. None of the bivariate residuals violated the conditional independence assumption (Table 4.3.6). The results are displayed in Figure 4.2.1; Table 4.2.3 contains the exact item response probabilities (RDS-weighted class sizes are presented in both; Table 4.3.7 provides unweighted estimates).

Table 4.2.3. Estimated item response probabilities of self-reported use of HIV prevention methods among the HIV-positive participants of the Engage-Montréal study, 2017–2018 (n=200): 3 class model[a]

Variable	Class 1: Mostly ART with viral suppression n=87 (53%, 95%CI: 41-65%)	Class 2: ART with viral suppression and condom use n=46 (19%, 95%CI:16-41%)	Class 3: ART with viral suppression and seroadaptive behavior use n=67 (18%, 95%CI: 10-27%)
ART with viral suppression	84%	86%	93%
Consistent condom use	0%	100%	15%
Strategic positioning	0%	29%	49%

Serosorting and/or PrEP sorting:			
Both	0%	8%	55%
PrEP sorting only	9%	0%	16%
Serosorting only	18%	3%	17%

Abbreviations: Antiretroviral treatment (ART); confidence interval (CI); pre-exposure prophylaxis (PrEP)

[a]RDS-II adjusted class sizes (%) and 95% confidence intervals are presented. RDS-II weights are inverse probability of sampling weights that are proportional to participant network size.

We labelled Class 1 as *mostly ART with viral suppression* (n=87), Class 2 as *ART with viral suppression and condom use* (n=46), and Class 3 as *ART with viral suppression and seroadaptive behavior use* (n=67). Among all classes, the proportion reporting a suppressed viral load was very high (84–93%). *Mostly ART with viral suppression,* the largest class, consisted of virally suppressed participants (84% probability) with a low or null probability of using any other prevention strategy of interest. Those in the *ART with viral suppression and condom use* class consistently used condoms (100% probability). Lastly, in the *ART with viral suppression and seroadaptive behavior use* class, participants performed serosorting and/or PrEP sorting, with a 55% probability of performing both, 16% probability of PrEP-sorting only, and 17% probability of serosorting only. This class also had a high probability (49%) of using strategic positioning.

Multinomial Logistic Regression Models

HIV-negative/unknown individuals

The referent class used was *low use of prevention*. The multivariable model indicates those in the *biomedical prevention use, condom use, and seroadaptive behaviour use* classes were more likely to report an increased number of anal sex partners (P6M) across all categories and having had an STBBI diagnosis (P12M) (Table 4.2.4; qualitative overview in Table 4.3.8). The *seroadaptive behaviour use* class members were further distinguished by being less likely to have an unknown HIV status (aOR: 0.5, 95%CI: 0.2–1.0). Those in the *biomedical prevention use* class were more likely to have obtained a post-high school

diploma or higher (aOR: 2.8, 95%CI: 1.5–5.3) and were also likely to have a main partner whose HIV-status is positive (aOR: 3.4, 95% CI: 1.0–11.4), perceived themselves less at risk of HIV (aOR: 0.5, 95%CI: 0.2–1.0), and had a higher HIV Optimism-Skepticism score (aOR: 1.1, 95%CI: 1.0–1.2).

Table 4.2.4. Univariable and multivariable multinomial logistic regression model results assessing factors associated with latent class membership among the HIV-negative/unknown participants of the Engage-Montréal study, 2017–2018 (n=968)[a]

Variable	Class 1: Biomedical prevention use		Class 2: Condom use		Class 3: Seroadaptive behavior use	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
Age ≤ 30	0.8 (0.5, 1.3)	0.7 (0.4, 1.3)	0.9 (0.7, 1.3)	0.8 (0.6, 1.2)	1.2 (0.8, 1.7)	0.9 (0.6, 1.4)
Sexual Orientation : Gay[b]	3.6 (1.7, 7.9)	0.8 (0.3, 2.0)	1.6 (1.1, 2.4)	1.3 (0.8, 2.2)	2.5 (1.5, 4.0)	1.3 (0.7, 2.4)
Ethnicity:						
French Canadian	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
English Canadian	0.6 (0.3, 1.4)	0.6 (0.2, 1.7)	0.9 (0.5, 1.6)	1.2 (0.7, 2.0)	1.1 (0.6, 2.0)	0.9 (0.5, 1.9)
European	1.9 (0.9, 4.0)	1.1 (0.4, 3.0)	2.5 (1.5, 4.1)	2.5 (1.4, 4.5)	2.9 (1.7, 5.1)	1.9 (1.1, 3.5)
Other	1.6 (0.9, 2.7)	1.1 (0.6, 2.2)	2.3 (1.5, 3.4)	2.4 (1.5, 3.8)	1.7 (1.1, 2.7)	1.4 (0.8, 2.4)
Education: post-high school diploma or higher	3.0 (1.8, 5.3)	2.8 (1.5, 5.3)	1.4 (1.0, 2.0)	1.1 (0.8, 1.6)	2.1 (1.4, 2.9)	1.4 (0.9, 2.1)

Variable	Class 1: Biomedical prevention use		Class 2: Condom use		Class 3: Seroadaptive behavior use	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
Social time spent with gay/bi guys: 50% or more	1.8 (1.2, 2.7)	0.8 (0.5, 1.4)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.7 (1.2, 2.4)	1.5 (1.0, 2.2)
HIV status: unknown	0.3 (0.1, 0.7)	0.6 (0.2, 1.9)	0.7 (0.4, 1.0)	0.8 (0.5, 1.5)	0.3 (0.1, 0.7)	0.5 (0.2, 1.0)
STBBI diagnosis in the past 12 months	11.0 (6.7, 18.1)	4.9 (2.6, 9.2)	1.7 (1.1, 2.6)	1.6 (1.0, 2.7)	4.3 (2.8, 6.8)	3.2 (1.9, 5.4)
Number of anal sex partners in the past 6 months:						
0-1	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
2-3	4.5 (1.5, 13.3)	6.5 (2.1, 20.2)	2.7 (1.8, 4.1)	2.6 (1.7, 4.1)	4.6 (2.8, 7.5)	4.2 (2.4, 7.1)
4-5	12.3 (3.9, 38.2)	13.1 (3.9, 43.6)	2.9 (1.6, 5.1)	2.5 (1.4, 4.7)	7.9 (4.3, 14.6)	6.1 (3.2, 11.7)
6+	67.9 (26.6, 173.4)	63.5 (23.1, 174.7)	3.2 (2.1, 5.0)	2.7 (1.6, 4.6)	10.5 (6.2, 17.7)	6.4 (3.6, 11.4)

Variable	Class 1: Biomedical prevention use		Class 2: Condom use		Class 3: Seroadaptive behavior use	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
HIV status of main partner:						
No main partner	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Unknown/ uncertain	0.2 (0.1, 0.6)	0.3 (0.1, 1.0)	0.7 (0.4, 1.1)	0.6 (0.4, 1.1)	0.7 (0.4, 1.3)	0.9 (0.5, 1.6)
HIV-negative	0.6 (0.4, 1.1)	1.1 (0.6, 2.0)	0.6 (0.4, 0.8)	0.5 (0.4, 0.8)	1.0 (0.7, 1.5)	1.3 (0.8, 2.0)
HIV-positive	2.2 (0.8, 5.6)	3.4 (1.0, 11.4)	0.4 (0.1, 1.1)	0.5 (0.1, 1.5)	0.7 (0.3, 2.1)	0.8 (0.3, 2.4)
Perceived risk of acquiring HIV	1.0 (0.6, 1.8)	0.5 (0.2, 1.0)	0.9 (0.6, 1.4)	0.7 (0.4, 1.2)	1.8 (1.2, 2.7)	1.3 (0.8, 2.2)
HIV Optimism-Skepticism Scale[c]	1.1 (1.1, 1.2)	1.1 (1.0, 1.2)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)
Currently have a health care provider	2.1 (1.3, 3.4)	2.1 (1.1, 3.9)	0.9 (0.6, 1.2)	1.1 (0.7, 1.5)	0.9 (0.6, 1.2)	1.0 (0.6, 1.4)

Variable	Class 1: Biomedical prevention use		Class 2: Condom use		Class 3: Seroadaptive behavior use	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95%CI)
Perceived mental health in the past 6 months:						
Excellent/very good	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Good	1.1 (0.7, 1.8)	1.6 (0.8, 3.0)	0.8 (0.5, 1.1)	0.8 (0.5, 1.2)	1.2 (0.8, 1.8)	1.4 (0.9, 2.2)
Fair/poor	1.1 (0.6, 2.0)	1.5 (0.7, 3.2)	0.6 (0.4, 0.9)	0.6 (0.4, 0.9)	0.9 (0.6, 1.4)	0.9 (0.5, 1.5)
Drug use: crack or cocaine in the past 6 months	1.4 (0.8, 2.3)	1.0 (0.5, 2.1)	0.8 (0.5, 1.1)	1.0 (0.6, 1.6)	1.1 (0.7, 1.6)	0.9 (0.6, 1.6)
Drug use: other drugs in the past 6 months[d]	2.9 (1.9, 4.6)	1.2 (0.6, 2.3)	0.9 (0.6, 1.2)	0.8 (0.5, 1.2)	1.7 (1.2, 2.4)	1.1 (0.7, 1.8)
Alcohol misuse: AUDIT-C Score ≥ 4[e]	0.9 (0.5, 1.3)	0.6 (0.3, 1.0)	0.7 (0.5, 1.0)	0.9 (0.6, 1.2)	1.2 (0.8, 1.7)	1.0 (0.7, 1.5)

Abbreviations: Odds ratio (OR); confidence interval (CI); adjusted odds ratio (aOR); sexually transmitted or blood borne infection (STBBI); Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C).

[a]Reference level: Class 4 – low use of prevention; confidence intervals account for clustering by participant recruiter.

[b]Sexual orientation was defined as gay versus other. The other terms used to describe one's sexual orientation included: bisexual, straight, queer, questioning, asexual, pansexual and two-spirit.

[c]The HIV Treatment Optimism-Skepticism Scale (62) includes items related to the efficacy of antiretrovirals for both HIV treatment and reduced infectiousness. The scale ranges from 0-36, where higher scores indicate higher optimism in antiretroviral treatment.

[d]Other drugs included any of ecstasy, crystal methamphetamine, mephedrone, speed, poppers, gamma hydroxybutyrate (GHB), lysergic acid diethylamide (LSD), and ketamine.

[e]Alcohol misuse was measured by the Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C), a screening tool for alcohol abuse, dependence, or heavy drinking (63). The AUDIT-C Scale ranges from 0-12, where higher scores indicate higher risk of alcohol affecting one's health and safety. Scores were dichotomized at the optimal cut point for identifying alcohol dependence in men (64): ≥4 vs. lower.

Individuals living with HIV

The referent class was mostly ART with viral suppression. The multivariable model indicates those in the ART with viral suppression and seroadaptive behavior use and ART with viral suppression and condom use classes were more likely to report an increased number of anal sex partners (P6M) across all categories (Table 4.2.5; qualitative overview in Table 4.3.9). The ART with viral suppression and condom use class members were also less likely to report having used other drugs (P6M; aOR: 0.2, 95%CI: 0.1–0.6) and less likely to have a higher HIV Optimism-Skepticism score (aOR: 0.9, 95%CI: 0.8–1.0). The ART with viral suppression and seroadaptive behavior use class members were more likely to have a post-high school diploma or higher (aOR: 2.4, 95%CI: 1.0–5.5).

Table 4.2.5. Univariable and multivariable multinomial logistic regression model results assessing factors associated with latent class membership among the HIV-positive participants of the Engage-Montréal study, 2017–2018 (n=200)[a,b]

Variable	Class 2: ART with viral suppression and condom use		Class 3: ART with viral suppression and seroadaptive behavior use	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95 CI)
Age ≤ 50	0.8 (0.4, 1.8)	1.9 (0.5, 6.4)	2.2 (1.2, 4.2)	1.5 (0.6, 3.6)
Sexual Orientation: Gay[c]	1.4 (0.5, 4.0)	1.9 (0.3, 11.7)	2.0 (0.7, 5.7)	1.4 (0.5, 4.5)
Ethnicity[d]:				
French Canadian	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
English Canadian	0.5 (0.1, 1.8)	1.1 (0.2, 5.3)	0.8 (0.3, 2.3)	0.6 (0.2, 2.2)
Other	1.3 (0.6, 2.8)	2.2 (0.8, 5.9)	1.0 (0.4, 2.3)	0.5 (0.2, 1.4)
Education: Post-high school diploma or higher	0.6 (0.3, 1.3)	0.5 (0.2, 1.3)	2.4 (1.3, 4.6)	2.4 (1.0, 5.5)
Social time spent with gay/bi guys: 50% or more	1.0 (0.5, 2.0)	1.0 (0.4, 2.5)	1.5 (0.8, 2.7)	1.1 (0.5, 2.5)
STBBI diagnosis in the past 12 months	0.5 (0.2, 0.9)	0.5 (0.2, 1.4)	1.8 (0.9, 3.4)	0.7 (0.3, 1.6)
Number of anal sex partners in the past 6 months:	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
0-1	2.0 (0.8, 5.5)	3.1 (0.8, 12.2)	8.6 (2.0, 36.2)	10.2 (1.6, 63.5)
2-3	0.9 (0.4, 2.1)	2.9 (0.8, 11.4)	13.3 (4.1, 42.9)	15.0 (3.1, 73.5)
4+				

Variable	Class 2: ART with viral suppression and condom use		Class 3: ART with viral suppression and seroadaptive behavior use	
	OR (95%CI)	aOR (95%CI)	OR (95%CI)	aOR (95 CI)
Currently have a main partner	0.8 (0.4, 1.6)	0.5 (0.2, 1.5)	0.6 (0.3, 1.2)	0.6 (0.2, 1.4)
HIV Optimism-Skepticism Scale[e]	0.9 (0.8, 0.9)	0.9 (0.8, 1.0)	1.0 (1.0, 1.1)	1.0 (0.9, 1.1)
Perceived mental health in the past 6 months:				
Excellent/very good	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Good	0.6 (0.3, 1.3)	0.5 (0.2, 1.3)	1.2 (0.5, 2.5)	0.8 (0.3, 2.2)
Fair/poor	0.4 (0.1, 1.0)	0.3 (0.1, 1.2)	1.4 (0.7, 2.8)	0.9 (0.3, 2.6)
Drug use: crack or cocaine in the past 6 months	0.6 (0.2, 1.4)	0.8 (0.2, 3.0)	1.0 (0.5, 2.2)	1.0 (0.4, 2.5)
Drug use: other drugs in the past 6 months[f]	0.3 (0.1, 0.6)	0.2 (0.1, 0.6)	3.4 (1.6, 7.3)	1.3 (0.5, 3.3)
Alcohol misuse: AUDIT-C Score ≥ 4[g]	0.5 (0.3, 1.1)	0.6 (0.2, 1.4)	1.0 (0.5, 1.8)	0.9 (0.4, 1.9)

Abbreviations: Antiretroviral treatment (ART); odds ratio (OR); confidence interval (CI); adjusted odds ratio (aOR); sexually transmitted or blood borne infection (STBBI); Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C).

[a]Reference level: Class 1 – Mostly ART with viral suppression; confidence intervals account for clustering by participant recruiter.

[b]The following variables could not be assessed in univariable or multivariable multinomial regression models due to small cell counts: HIV status of current main partner, perceived risk of transmitting HIV, and currently have a health care provider.

[c]Sexual orientation was defined as gay versus other. The other terms used to describe one's sexual orientation included: bisexual, straight, queer, questioning, asexual, pansexual and two-spirit.

[d]Ethnicity is redefined in these models as French Canadian, English Canadian, and other (including European) due to small cell counts.

[e]The HIV Treatment Optimism-Skepticism Scale (62) includes items related to the efficacy of antiretrovirals for both HIV treatment and reduced infectiousness. The scale ranges from 0-36, where higher scores indicate higher optimism in antiretroviral treatment.

[f]Other drugs included any of ecstasy, crystal methamphetamine, mephedrone, speed, poppers, gamma hydroxybutyrate (GHB), lysergic acid diethylamide (LSD), and ketamine.

[g]Alcohol misuse was measured by the Alcohol Use Disorders Identification Test, consumption questions (AUDIT-C), a screening tool for alcohol abuse, dependence, or heavy drinking (63). The AUDIT-C Scale ranges from 0-12, where higher scores indicate higher risk of alcohol affecting one's health and safety. Scores were dichotomized at the optimal cut point for identifying alcohol dependence in men (64): ≥4 vs. lower.

Discussion

The combination of prevention strategies targeting different transmission pathways is our best option to sustainably reduce HIV incidence. We assessed combination prevention at the individual level, where strategies practiced by GBM might vary within and across sexual partners or experiences (14, 69). In Montréal, we found condoms remain a preferred strategy used by many GBM, but antiretroviral-based prevention methods are now distinctly reported. The proportion of GBM who are living with HIV and aware of their status with a suppressed viral load was very high for all combination prevention classes (84-93%), indicating diagnosed GBM living with HIV in Montréal are being engaged into HIV care. However, we also observed that 9% of GBM reported not knowing if they were HIV-negative or -positive, underscoring the importance of reaching those GBM for HIV testing, as diagnosing those unaware they are living with HIV is essential for treatment-as-prevention to be effective. These testing encounters could also be an opportunity for health care providers to discuss current prevention strategies with GBM. Among HIV-negative/unknown GBM, an estimated 7% belonged to the class adopting *biomedical*

prevention, 84% of which reported PrEP use. Yet, among HIV-negative GBM overall, this level of PrEP coverage may be too low to sustainably reduce HIV incidence (70-72). In general, the patterns we observed suggest that within classes of prevention users, especially in HIV-negative GBM, the combining of different prevention types was limited. Ensuring both HIV-negative GBM and GBM living with HIV are aware of and have access to many of today's tools would allow them to determine which strategies will meet their needs in different situations. This could increase the adoption of multiple strategies and the individual-level use of combination prevention. Further, for combination prevention to be effective at the population-level, matching appropriate strategies to the risk profiles of GBM must be promoted. Increasing healthcare provider awareness of and sensitivity to these profiles would also be essential, to assist in their approach to patient engagement in preventive care and encourage appropriate conversations around U=U and PrEP.

Correlates of class membership suggest HIV-negative/unknown GBM with an increased number of anal sex partners or reported STBBI diagnosis are more commonly in classes of *biomedical prevention use, condom use*, and *seroadaptive behavior use*. For the *condom use* class, in particular, the association with an STBBI diagnosis presents an apparent discordance, despite the uncertainty in this estimate; however, it is possible that receiving an STBBI diagnosis led to the use of condoms consistently. Those in the remaining subgroup, who use fewer prevention strategies, are ultimately at a lower risk of HIV acquisition. Among this class, 27% of GBM reported not having any anal sex partners in the P6M, and 33% had only one. Despite this, the risk among GBM in this group is not necessarily null and some might be missed in the reach of current prevention programs. The *biomedical prevention use* class had higher optimism in ART and reported feeling less at risk for HIV acquisition while being more likely to have a main partner whose HIV-status is positive, suggesting a higher prevention awareness among these HIV-negative GBM, perhaps through their experience of having a partner that is living with HIV. This may also be explained by the fact these men were more likely to have attained a higher level of education, possibly having a higher level of health literacy as well. Community-based promotion of antiretroviral-based prevention could, therefore, be needed to inform GBM of their effective protection against HIV transmission more widely. Among GBM living with HIV, we similarly identified subgroups of *ART with viral suppression and*

condom use and *ART with viral suppression and seroadaptive behavior use* more likely to have an increased number of anal sex partners. We also observed a subgroup using biomedical prevention (*ART with viral suppression*) alone. Members of this class did have a high probability of a suppressed viral load, suggesting U=U is appropriately being practiced by this class; however, whether these GBM explicitly consider their use of ART as a prevention strategy is not known.

Our results are generally consistent with the previous Montréal study that identified subgroups of HIV-negative/unknown GBM adopting condoms and various seroadaptive strategies (32). Our analyses, however, suggest the emergence of a new class of combination prevention among HIV-negative/unknown GBM using antiretroviral-based prevention strategies, especially PrEP. Notably, members of this class had a somewhat low probability of using condoms consistently (34%), in-line with indications for initiating PrEP in Québec (condomless anal sex in the P6M and one additional risk factor for HIV acquisition) (73), as well as the known efficacy of PrEP, and supported by findings from a clinical cohort of PrEP users in Montréal (74). PrEP can also be among the strategies GBM living with HIV might use – they can perform PrEP sorting, whereby they consider the PrEP-status of HIV-negative GBM when choosing such sexual partners (75). In our study, we also saw a high proportion of GBM living with HIV adopting seroadaptive behaviors by choosing to have condomless anal sex with GBM living with HIV or HIV-negative GBM on PrEP. Neither these, nor PrEP use, however, prevent the transmission of other STBBIs and their utilization alone could have implications on their spread within GBM (76, 77), especially as these sub-groups had a low probability of condom use.

Studies elsewhere also used LCA to investigate prevention use among various populations of GBM. These mainly focused on serosorting and seropositioning (33, 42, 43). While these are well known to be practiced by GBM across various settings (11-17), their level of use is expected to differ in our study, given the additional strategies we assessed and our consideration of viral load and PrEP sorting. Further, the use of seroadaptive practices could be lower among antiretroviral medication users. Only Dangerfield et al. (42) assessed seroadaptive strategies in a time of PrEP availability. Qualitatively similar to our results, this study found the majority of Paris GBM belonged to a class defined by a low number

of condomless anal sex acts. To our knowledge, few other studies of GBM have assessed such a variety of biomedical HIV prevention strategies (77-80). Studies conducted in France, Australia, and the United States assessed time trends in prevention use by GBM (77-79). In line with our findings, all observed that, despite decreases, consistent condom use remained a dominant strategy in recent years, and the use of antiretroviral-based strategies was increasing (77-79). Regarding biomedical seroadaptive behaviors, Grov et al. (80) also considered these and witnessed PrEP and viral load sorting taking place among GBM in the United States.

This study has several limitations. First, like previous studies on this topic (32, 33), our results are limited by self-reported measures, which could be influenced by a social desirability bias and imperfect recall. This bias could lead to an overestimation of any prevention strategy use; however, use of a computer-assisted questionnaire likely helped mitigate this (81). Second, the nature of prevention is dynamic, with an individual's adoption of various strategies changing over time, based on their perceived risk of HIV acquisition or transmission. Using a recall period of the P6M for many of the prevention indicators may be too limited to capture this reality entirely. A longitudinal assessment of combination prevention is needed, which Engage could perform in the future. Third, given the cross-sectional nature of our RDS survey, temporality between measures cannot be inferred. For instance, we cannot claim whether the low proportion having used condoms in the P6M is a reason for initiating, or a consequence of, PrEP use. Fourth, we considered recreational drug and alcohol use in our analyses. However, situational use of drugs or alcohol during sex are also important factors related to use of prevention, and these were not assessed. Lastly, as an exploratory analysis investigating many correlates of class membership, the precision of the regression estimates was reduced. Future analyses including participants from all Engage sites would likely improve the precision of estimates and would allow for an examination of whether classes vary by city.

The study strengths include the large sample of GBM and method of recruitment, RDS, which may improve its representativeness. The comprehensive study questionnaire enabled the collection of information on several relevant biomedical and behavioral prevention strategies. Again, the results we observed are consistent with the previous work in

Montréal, with the emergence of a new class among HIV-negative/unknown GBM being plausible given the evolving nature of prevention and its accessibility. Importantly, eliminating HIV will not be achieved without fully appreciating transmission dynamics and the need for prevention use by both HIV-negative and GBM living with HIV. In this study, we viewed prevention broadly, adopting an HIV status-neutral approach and assessing prevention strategies acting on both HIV transmission and acquisition.

Conclusions

The number of HIV diagnoses among GBM in Canada has remained relatively stable in recent years. Achieving the UNAIDS Fast-Track city targets in Montréal will require the scale-up of combination HIV prevention strategies meeting the needs of both HIV-negative GBM and GBM living with HIV. With combination prevention, individuals identify the HIV prevention strategies best suited for them. This LCA of combination prevention is the first to include PrEP use and, indeed, demonstrated its emergence as a distinct prevention strategy used by Montréal GBM. Our finding that the HIV-negative/unknown GBM currently using biomedical prevention are those with a higher level of formal education is important. This observation, in conjunction with biomedical prevention use being the smallest class of HIV-negative/unknown GBM, indicates the need to continue to raise awareness of PrEP's effectiveness and to promote its availability for HIV at-risk GBM. Moreover, despite medication reimbursement for PrEP in Québec, out-of-pocket costs (up to $93/month) could be a barrier to PrEP access which should be further assessed. Identifying sub-groups of GBM highly vulnerable to HIV transmission and tailoring appropriate combination prevention programs to their needs will also be important.

Future work should use longitudinal data to assess the consistency of these results and monitor potential variability in prevention over time. The implications of HIV prevention strategies on STI transmission in Montréal should also be examined, particularly among those using mainly seroadaptive behaviors or PrEP, as GBM may not be consistently using condoms when utilizing these measures.

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Ethics

Ethics approval for the Engage Study in Montréal was obtained from the Research Institute of the McGill University Health Centre. Ethics approval for the Engage Study co-authors outside of Montréal was obtained from Ryerson University, the University of Windsor, St. Michael's Hospital, the University of Toronto, the University of British Columbia, Simon Fraser University, and the University of Victoria.

Consent to participate

Informed consent was obtained from all individual participants included in the study. The age of consent to participate in a research study in all Canadian provinces, excluding Québec, is 16 (82). Within the province of Québec, the age of consent to participate is 18 (82). Following guidelines provided by *the Society for Adolescent Medicine* (83), Engage did not seek parental consent of those aged 16-18 in Montréal. Those aged 14 and older can legally consent to STBBI screening in Québec without parental consent (84), and responding to the Engage questionnaire would be of minimal risk to GBM aged 16-18. On the other hand, as a study of sexual health among sexually active GBM, requiring parental

consent could compromise the privacy, and possibly safety, of young GBM. Therefore, the potential harms of seeking parental consent to participate in the Engage study for GBM aged 16-18 outweighed the harms of not obtaining parental consent.

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4.3. Manuscript 1: Supplementary Materials

4.3.1. Appendix 1

Additional details on the use of respondent-driven sampling (RDS) in the 2017-2018 Engage-Montréal study, according to the Strobe-RDS guidelines (1)

Study setting

The primary purpose of the Engage study is to have an updated understanding of the sexual health of gay, bisexual, queer and other men who have sex with men (GBM), including transmen, in order to support HIV and other sexually transmitted or blood-borne infection (STBBI) prevention efforts (2). The Engage study utilized RDS to obtain a representative sample of GBM at each study site (Montréal, Toronto, and Vancouver). In Montréal, participant recruitment and data collection took place between February 2017–June 2018 at a community-based study site.

Formative research findings

Prior to study initiation, formative research involving engagement and consultation with local community organizations and individual community members was carried out by the study investigators. This formative work aided in identifying a diverse group of study seeds, validating study procedures, and creating promotional materials.

Seed selection

With RDS, initial participants (or 'seeds') are purposively selected such that they are eligible for the study, socially connected to many members of the population, and altogether characterize diverse features of the population in order to access its various subgroups (3). In Engage, selected seeds were required to self-report as motivated to recruit additional participants into the study and know a minimum of six other GBM that would satisfy the study eligibility criteria. To obtain a diverse sample, 25 seeds of varying age, HIV status, gender identity, and ethnicity were initially selected. Monitoring of the participant sample composition was performed throughout the recruitment and data collection period, which allowed the study investigators to assess the progress of the RDS recruitment and potential need for additional seeds. Throughout recruitment in Montréal, two additional seeds were added in order to capture younger GBM in the study sample.

RDS recruitment

The process of RDS recruitment was explained to all participants by an onsite study staff member (either a research assistant or study nurse). Beginning with the seeds, participants were provided with six coupons to distribute to eligible and interested GBM that had not already participated in the study. Those who did participate were compensated with $50, as well as $15 for each successful recruit. The option to forego the $50 and instead enter into a draw for a $250 prepaid credit card or a $2000 travel voucher was also provided to all participants. In general, there were no time limits set for referrals; however, in the last two months of recruitment (April-May 2018), participants distributing coupons were informed that the recruitment period would end by June 2018. Those who participated in the last three weeks of the recruitment period were not provided with any invitation coupons.

Eligibility

All potential participants were screened over the phone or onsite for eligibility by a research coordinator or study nurse. Study eligibility criteria included:

1. Gender identify as a man, including transgender man
2. ≥16 years
3. Had sex with another man in the past six months
4. Reside in the greater Montréal area, and
5. Able to read in French or English.

Participant database

A participant database containing information on each participant, including their name, contact information, study identification number, referrer identification number, and coupon numbers (for each of the six coupons issued) was established. This database was monitored and updated continuously to ensure that repeat enrollments did not occur.

Study sample

Engage aimed to enroll 1000 participants at the Montréal site. Upon completion of the recruitment process a total of 1179 eligible GBM had participated in Montréal. The number of coupons issued and returned were 6822 and 1152, respectively.

Self-reported personal network size

The following question was used to obtain information on participant personal network size in the Engage questionnaire: "*How many men who have sex with men aged 16 years or older, including trans men, do you know who live or work in the [Metro Vancouver/Greater Toronto/Metro Montréal depending on site] area (whether they identify as gay or otherwise)? This includes gay/bi guys you see or speak to regularly; e.g., close friends, boyfriends, spouses, regular sex partners, roommates, relatives, people you regularly hang out with, etc.*"

Recruiter-recruit relationship

Unique identification numbers were assigned to each participant, and the information on who recruited whom was tracked by recording the recruiter's identification number in the study participant database.

Study Analyses

Study seeds were included in all analyses. In this study, RDS adjustments of the sociodemographic characteristics and latent class sizes were made using the RDS-II estimator. This estimator weights the sample proportions by the inverse of the self-reported participant network size.

4.3.2. Appendix 2

Survey questions corresponding to the self-reported measures of combination HIV prevention methods examined in this study.

Table 4.3.1. Survey items from the 2017-2018 Engage study questionnaire used to measure HIV prevention methods according to HIV status

Prevention Method[a]	Survey Question
HIV-negative/unknown	
Recent HIV testing[b]	*When were you last tested for HIV?*
PEP use[b]	*Have you ever taken PEP?*
PrEP use[b]	*Have you ever taken PrEP yourself?*
Consistent condom use[b]	*Some HIV negative guys use strategies to prevent getting HIV. Have you done any of the following to prevent getting HIV in the past 6 months? → Always used condoms for anal sex*
Strategic positioning[b]	*Some HIV negative guys use strategies to prevent getting HIV. Have you done any of the following to prevent getting HIV in the past 6 months? → Being the top (insertive partner) for anal sex*
Serosorting	*Some HIV negative guys use strategies to prevent getting HIV. Have you done any of the following to prevent getting HIV in the past 6 months? → Had sex without condoms with guys I know are HIV-negative*
Viral load sorting	*Some HIV negative guys use strategies to prevent getting HIV. Have you done any of the following to prevent getting HIV in the past 6 months? → Had sex without condoms with HIV-positive guys who have 'undetectable' (low) viral loads*
Serosorting or viral load sorting[b]	*As above.*
HIV-positive	
ART with viral suppression[c]	*AT THIS TIME, what do you think your HIV viral load is?* → *Undetectable (>50 copies/mL)*
Consistent condom use[c]	*Some HIV-positive guys use strategies to prevent transmitting HIV to their sex partners. Have you done any of the following to prevent your sex partners from getting HIV in the past 6 months?* → *Always used condoms for anal sex*

Strategic positioning[c]	*Some HIV-positive guys use strategies to prevent transmitting HIV to their sex partners. Have you done any of the following to prevent your sex partners from getting HIV in the past 6 months?* *→ Being the bottom (receptive partner) for anal sex*
Serosorting	*Some HIV-positive guys use strategies to prevent transmitting HIV to their sex partners. Have you done any of the following to prevent your sex partners from getting HIV in the past 6 months?* *→ Had sex without condoms with guys I know are HIV-positive*
PrEP-use sorting	*Some HIV-positive guys use strategies to prevent transmitting HIV to their sex partners. Have you done any of the following to prevent your sex partners from getting HIV in the past 6 months?* *→ Had sex without condoms with HIV-negative guys who are using PrEP*
Serosorting and/or PrEP-use sorting[c]	*As above.*

Abbreviations: Post-exposure prophylaxis (PEP); pre-exposure prophylaxis (PrEP); antiretroviral treatment (ART).

[a]Use of each prevention method was measured in the past 6 months, except for PEP (ever use) and ART with viral suppression (current).

[b]Used as an indicator in HIV-negative/unknown latent class analysis models.

[c]Used as an indicator in HIV-positive latent class analysis models.

4.3.3. Appendix 3

Additional tables of study results

Table 4.3.2. Model fit statistics of all latent class models performed on self-reported use of HIV prevention methods among the HIV-negative/unknown participants of the Engage-Montréal study, 2017–2018 (n=968)

Model	Log-likelihood	Residual df	BIC	AIC	LR	Entropy
1 class	-3366.955	57	6775.161	6745.909	445.517	3.48
2 class	-3211.355	50	6512.088	6448.710	134.318	3.33
3 class	-3180.187	43	6497.878	6400.373	71.981	3.30
4 class	-3161.094	36	6507.820	6376.189	33.797	3.27
5 class	-3155.503	29	6544.765	6379.007	22.615	3.26

Abbreviations: Degrees of freedom (df); Bayes Information Criterion (BIC); Akaike Information Criterion (AIC); likelihood ratio (LR)

Table 4.3.3. Bivariate residuals between item pairs of self-reported use of HIV prevention methods among the HIV-negative/unknown participants of the Engage-Montréal study, 2017–2018 (n=968): 4 class model

Variable	HIV testing	PrEP	PEP	Condom	Strategic positioning
HIV testing					
PrEP	0.33				
PEP	0.05	0.05			
Condom	0.02	0.09	0.09		
Strategic positioning	0.02	0.05	0.18	1.02	
Serosorting or viral load sorting	0.03	0.10	0.10	0.55	0.20

Abbreviations: Pre-exposure prophylaxis (PrEP); post-exposure prophylaxis (PEP).

Table 4.3.4. Unadjusted and RDS-II adjusted class sizes of the 4-class model of self-reported use of HIV prevention methods among the HIV-negative/unknown participants of the Engage-Montréal study, 2017 – 2018 (n=968)[a]

Class	Unweighted estimate	RDS-II weighted estimate (95%CI)
1: Biomedical prevention use	12%	7% (4-10%)
2: Condom use	35%	40% (34-45%)
3: Seroadaptive behavior use	25%	21% (17-26%)
4: Low use of prevention	28%	32% (27-37%)

Abbreviations: Respondent driven sampling weights (RDS-II); confidence interval (CI).

[a]RDS-II weights are inverse probability of sampling weights that are proportional to participant network size.

Table 4.3.5. Model fit statistics of all latent class models performed on self-reported use of HIV prevention methods among the HIV-positive participants of the Engage-Montréal study, 2017–2018 (n=200)

Model	Log-likelihood	Residual df	BIC	AIC	LR	Entropy
1 class	-547.972	25	1127.733	1107.943	61.564	21.92
2 class	-532.371	18	1133.620	1090.742	30.363	21.28
3 class	-524.167	11	1154.300	1088.333	13.954	20.98

Abbreviations: Degrees of freedom (df); Bayes Information Criterion (BIC); Akaike Information Criterion (AIC); likelihood ratio (LR)

Table 4.3.6. Bivariate residuals between item pairs of self-reported use of HIV prevention methods among the HIV-positive participants of the Engage-Montréal study, 2017–2018 (n=200): 3 class model

Variable	Viral suppression	Condom	Strategic positioning
Viral suppression			
Condom	1.40		
Strategic positioning	1.44	0.35	
Serosorting and/or PrEP sorting	0.78	0.26	0.39

Abbreviations: Pre-exposure prophylaxis (PrEP)

Table 4.3.7. Unadjusted and RDS-II adjusted sizes of the 3-class model of self-reported use of HIV prevention methods among the HIV-positive participants of the Engage-Montréal study, 2017–2018 (n=200)[a]

Class	Unweighted estimate	RDS-II weighted estimate (95% CI)
1: Mostly ART with viral suppression	44%	53% (41-65%)
2: ART with viral suppression and condom use	23%	19% (16-41%)
3: ART with viral suppression and seroadaptive behavior use	34%	18% (10-27%)

Abbreviations: Respondent driven sampling weights (RDS-II); confidence interval (CI); antiretroviral treatment (ART).

[a]RDS-II weights are inverse probability of sampling weights that are proportional to participant network size.

Table 4.3.8. Overview of multivariable multinomial logistic regression model results assessing factors associated with latent class membership among the HIV-negative/unknown participants of the Engage-Montréal study, 2017–2018 (n=968)[a]

Class 1: Biomedical prevention use	Class 2: Condom use	Class 3: Seroadaptive behavior use
–	↑ European ethnicity	↑ European ethnicity[b]
–	↑ Other ethnicity	–
↑ Education	–	–
–	–	↑ Spend 50% or more of social time with gay/bi guys[b]
–	–	↓ Unaware of HIV status[c]
↑ STBBI diagnosis in past 12 months	↑ STBBI diagnosis in last 12 months[b]	↑ STBBI diagnosis in past 12 months
↑ 2-3 anal sex partners in past 6 months	↑ 2-3 anal sex partners in past 6 months	↑ 2-3 anal sex partners in past 6 months
↑ 4-5 anal sex partners in past 6 months	↑ 4-5 anal sex partners in past 6 months	↑ 4-5 anal sex partners in past 6 months
↑ 6+ anal sex partners in past 6 months	↑ 6+ anal sex partners in past 6 months	↑ 6+ anal sex partners in past 6 months
↓ Have a main partner they were certain was HIV-negative[c]	↓ Have a main partner they were certain was HIV-negative	–
↑ Have a main partner they were certain was HIV-positive[b]	–	–
↓ Perceived risk of HIV[c]	–	–
↑ score on HIV Optimism-Skepticism Scale[b]	–	–
↑ Health care provider	–	–
–	↓ Report in fair/poor mental health in the past 6 months	–
↓ Alcohol misuse[c]	–	–

Abbreviations: Sexually transmitted or blood borne infection (STBBI)

[a]Reference level: Class 4 – Low use of prevention

[b]An imprecise association, yet indicative of an increased odds.

[c]An imprecise association, yet indicative of a decreased odds.

Table 4.3.9. Overview of multivariable regression multinomial logistic model results assessing factors associated with latent class membership among the HIV-positive participants of the Engage-Montréal study, 2017 – 2018 (n=200)[a]

Class 2: ART with viral suppression and condom use	Class 3: ART with viral suppression and seroadaptive behavior use
–	↑ Education[b]
↓ STBBI diagnosis in past 12 months[c]	–
↑ 2-3 anal sex partners in past 6 months[b]	↑ 2-3 anal sex partners in past 6 months
↑ 4+ anal sex partners in past 6 months[b]	↑ 4+ anal sex partners in past 6 months
↓ HIV Optimism-Skepticism score[c]	–
↓ Use of other drugs in past 6 months	–

Abbreviations: Antiretroviral treatment (ART); sexually transmitted or blood borne infection (STBBI)

[a]Reference level: Class 1 – Mostly ART with viral suppression.

[b]An imprecise association, yet indicative of an increased odds.

[c]An imprecise association, yet indicative of a decreased odds.

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Chapter 5. Manuscript 2

5.1. Preface to Manuscript 2

In Manuscript 1, I found that antiretroviral-based prevention became a prominent feature of the combination HIV prevention landscape for Montréal gbMSM by 2018. However, there remain many unknowns about the population-level impacts of PrEP use in Québec. For instance, how many HIV acquisitions it averted, if usage could have been optimized, and whether higher coverage would have been required to affect transmission dynamics. To this end, I evaluated the population-level impact of PrEP over 2013-2021 using a mathematical model of HIV transmission among Montréal gbMSM. Such mathematical models enable an understanding of the direct benefits of PrEP in preventing acquisition among users but also the indirect benefits accrued through decreased population prevalence of unsuppressed viral load among gbMSM not on PrEP. All co-authors have reviewed this manuscript, and it has been submitted to a peer-reviewed journal.

5.2. Manuscript 2: Population-level impact of pre-exposure prophylaxis on HIV acquisition and transmission among men who have sex with men: a mathematical modeling study in Montréal, Canada (2013-2021)

Carla M Doyle[1], Rachael M Milwid[1], Joseph Cox[1,2,3], Yiqing Xia[1], Gilles Lambert[2], Cécile Tremblay[4,5], Joanne Otis[6], Marie-Claude Boily[7], Jean-Guy Baril[8,9], Réjean Thomas[10], Alexandre Dumont Blais[11], Benoit Trottier[9], Daniel Grace[12], David M. Moore[13, 14], Sharmistha Mishra[15, 16, 17], Mathieu Maheu-Giroux[1§]

[1]Department of Epidemiology and Biostatistics, School of Population and Global Health, McGill University, Montréal, QC

[2]Direction Régionale de Santé Publique de Montréal, Montréal, QC

[3]Clinical Outcomes Research and Evaluation, Research Institute - McGill University Health Centre, Montréal, QC

[4]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC

[5]Département de Microbiologie, Infectiologie et Immunologie, Université de Montréal, Montréal, QC

[6]Département de Sexologie, Université du Québec à Montréal, Montréal, QC

[7]MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK

[8]Department of Family Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, QC

[9]Clinique de médecine urbaine du Quartier Latin, Montréal, QC

[10]Clinique médicale l'Actuel, Montréal, QC

[11] RÉZO, Montréal, QC

[12]Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[13]BC Centre for Excellence in HIV/AIDS, Vancouver, BC

[14]Faculty of Medicine, University of British Columbia, Vancouver, BC

[15]Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON

[16]*Institute of Medical Sciences, University of Toronto, Toronto, ON*

[17]*Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON*

[§]**Corresponding Author:** Mathieu Maheu-Giroux

Address for Correspondence: mathieu.maheu-giroux@mcgill.ca

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Availability of data and materials: The data that support the findings of this study are available from *Engage*. These data are not publicly available and restrictions do apply for access. *Engage* permitted the use of these data for this study. The data could be available from the authors upon reasonable request and with permission of *Engage*.

Authors Contributions: CMD, RMM, MM-G, and JC contributed to the study conception and design. RMM, CMD, YX, and MM-G contributed to model development, parameterization, and calibration. JC, GL, DMM, DG, and RT were involved in the data collection. Analyses were performed by CMD, with support from MM-G, JC, and RMM. The manuscript was drafted by CMD. All authors contributed to the interpretation of results and reviewed the manuscript for important intellectual content. Overall supervision for this project was provided by MM-G and JC. All authors approved the final manuscript.

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Abstract

Introduction: HIV pre-exposure prophylaxis (PrEP) has been recommended and partly subsidized in Québec, Canada, since 2013. We evaluated the population-level impact of PrEP on HIV transmission among men who have sex with men (MSM) in Montréal, Québec's largest city, over 2013-2021.

Methods: We used an agent-based mathematical model of sexual HIV transmission to estimate the fraction of HIV acquisitions averted by PrEP compared to a counterfactual scenario without PrEP. The model was calibrated to local MSM survey, surveillance, and cohort data and accounted for COVID-19 pandemic impacts on sexual activity, prevention, and care. PrEP was modelled from 2013 onward, assuming 86% individual-level effectiveness. The PrEP eligibility criteria were: any anal sex unprotected by condoms (past six months) and either multiple partnerships (past six months) or multiple uses of post-exposure prophylaxis (lifetime). To assess potential optimization strategies, we modelled hypothetical scenarios prioritizing PrEP to MSM with high sexual activity (≥11 anal sex partners annually) or aged ≤45 years, increasing coverage to levels achieved in Vancouver, Canada (where PrEP is free-of-charge), and improving retention.

Results: Over 2013-2021, the estimated annual HIV incidence decreased from 0.4 (90% credible interval [CrI]: 0.3-0.6) to 0.2 (90%CrI: 0.1-0.2) per 100 person-years. PrEP coverage in HIV-negative MSM remained low until 2015 (<1%). Afterward, coverage increased to a maximum of 10% of all HIV-negative MSM and 16% of the 62% PrEP-eligible HIV-negative MSM in 2020. Over 2015-2021, PrEP averted an estimated 20% (90%CrI: 11%-30%) of cumulative HIV acquisitions. The hypothetical scenarios modelled showed that, at the same coverage as the provincial intervention, prioritizing PrEP to MSM with high sexual activity could have averted 30% (90%CrI: 19%-42%) of HIV acquisitions from 2015-2021. Even higher impacts could have resulted from higher coverage. Under the provincial eligibility criteria, reaching 10% coverage among HIV-negative MSM in 2015 and 30% in 2019, like attained in Vancouver, could have averted up to 63% (90%CrI: 54%-70%) of HIV acquisitions from 2015-2021.

Conclusions: PrEP reduced population-level HIV transmission among Montréal MSM. However, our study suggests missed prevention opportunities and adds support for public policies that provide PrEP free-of-cost to MSM at risk of HIV acquisition.

Introduction

After over 20 years under study[1-3] and ten years of availability[4], oral pre-exposure prophylaxis (PrEP) has proven highly efficacious for preventing HIV acquisition across transmission routes. Rigorous randomized controlled clinical and pragmatic trials and other observational data speak directly to its prevention benefits among men who have sex with men (MSM) when taken daily or on-demand[5-10]. The IPERGAY trial in Canada (Québec) and France showed an 86% (95% confidence interval [CI]: 40%-98%) efficacy in preventing HIV acquisition among MSM assigned to on-demand oral PrEP compared to placebo[6]. Furthermore, its open-label extension study suggested that effectiveness could increase to 97% (95%CI: 81%-100%) among fully adherent on-demand PrEP users[8]. However, limited research as examined PrEP's real-world impact on HIV dynamics over years of implementation, and all existing studies were empirical studies relying on observed HIV diagnoses[11, 12], which can be affected by testing efforts.

Individual-based trials are important to demonstrate individual-level effectiveness but cannot provide the effect size estimates of public health relevance: the population-level relative decline in HIV incidence. Beyond the direct prevention benefits to PrEP users, the population-level effects include the indirect gains accrued by individuals not taking PrEP, who are at reduced risk of HIV acquisition as PrEP interrupts transmission chains and diminishes the number of their contacts able to transmit HIV. However, estimating this population-level effect empirically can be methodologically challenging, as the ongoing dynamics of HIV transmission and the use of other prevention tools can make it difficult to define suitable control groups. In Québec, concomitant 2013-2015 changes in antiretroviral treatment (ART) guidelines to immediate initiation and strengthened "undetectable=untransmittable" messaging especially complicate this. Under these circumstances, mathematical modelling can be advantageous[13].

Québec implemented interim guidelines for tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) as HIV PrEP in 2013[14], the only province/territory to do so ahead of Health Canada's licencing in 2016 and the development of national PrEP guidelines in 2017[15]. These guidelines recommended PrEP for MSM that had condomless anal sex in the past six months and met one of the following criteria related to sexual behaviour: 1) two or

more sex partners in the past six months, 2) history of repeated post-exposure prophylaxis (PEP) use, 3) history of syphilis or an anal bacterial sexually transmitted infection, 4) sex with a partner living with HIV whose risk of transmission is considered high, or 5) psychoactive substance use during sex[14, 16, 17]. At the same time, Québec's drug insurance program included TDF-FTC as PrEP in its formulary, reducing its cost to a monthly co-payment of up to CAD$96.74[18]. However, nearly a decade later, PrEP's impact on the local HIV epidemic has not yet been evaluated, partly due to the aforementioned challenges. Such evaluations are essential for understanding PrEP's role in eliminating HIV as a public health threat and improving its delivery.

With over two million people, Montréal is Québec's largest city[19] and the epicentre of its HIV epidemic[20]. It was the first city in Canada to join the Fast-Track Cities initiative, aiming to eliminate HIV[21], and has well-established HIV surveillance and population-based data for monitoring the HIV response. Leveraging these data, we evaluated the population-level effectiveness of PrEP on HIV transmission among MSM in Montréal over 2013-2021 and investigated if and how this intervention could have been optimized. Our analysis employed a mathematical model to disentangle the unique contribution of PrEP from other interventions and simulate an appropriate counterfactual scenario. PrEP is pillar of HIV elimination efforts[22] and preferred prevention method for many Canadian MSM[23]. Understanding the impact of PrEP can guide decision-makers in accelerating the city's progress toward zero new HIV acquisitions.

Methods

Model overview

We used an existing calibrated agent-based model of sexual HIV transmission among Montréal MSM, described elsewhere[24]. Briefly, it is a stochastic, mechanistic model including several modules to simulate demographics, partnership formation and dissolution (i.e., casual and regular sex partnerships, and mixing by age, serostatus, and preferred insertive/receptive role during anal sex), use of HIV prevention tools (i.e., condoms, PEP, PrEP, and viral suppression), the HIV treatment and care cascade (i.e., HIV testing and ART), HIV transmission, and disease progression[24]. Initialized in 1975, the model tracks a population of 10,000 MSM aged 15+ years that increases over time, reflecting Montréal's

demographics. Men are categorized by age (15-24, 25-34, 35-44, 45-54, 55+ years) and sexual activity level (low, medium, and high, with 0-5, 6-10, and 11+ sexual partners per year, respectively), and exit the model due to death from natural or HIV/AIDS-related causes. The model is implemented in R (v.4.1.0) with a C++ back-end using the Rcpp library[25-27], and simulated with a two-week time step.

We calibrated the model to the following sexual behaviour, epidemic, and intervention outcomes: the distribution of the number of anal sex partners in the past six months, prevalence and duration of regular partnerships, CD4 cell count at diagnosis by year (2013-2017), HIV prevalence by age (18-29, 30-49, 50+ years) and year (2005, 2008, 2017-2019), the prevalence of lifetime PrEP use by year (2017-2019), PrEP coverage (defined as the proportion currently using PrEP among those not living with HIV) by year (2017-2019), the proportion of people living with HIV (PLHIV) diagnosed by year (2005, 2008, 2017), and ART coverage among PLHIV by year (2005, 2017-2018). Using an Approximate Bayesian Computational Sequential Monte Carlo fitting method[28, 29], we obtained 100 calibrated parameter sets of the 54 parameters governing transmission and can reproduce the observed epidemic dynamics.

PrEP-related data sources

We used data from two sources to parameterize and calibrate the PrEP module (Table 5.2.1). The *Engage Cohort*[30], a population-based study of sexually active MSM aged 16+ years in Montréal, Toronto, and Vancouver, provided data from 2017-2021. In Montréal, a closed cohort of men that had sex with another man in the past six months were recruited over 2017-2018 (N=1,179) by respondent-driven sampling (RDS) and visits occurred annually until 2021. The *l'Actuel PrEP Cohort*[31], an ongoing clinical cohort at Montréal's *Clinique l'Actuel*, provided data on individuals consulting for and prescribed PrEP from 2013-2019 (N=2,746, 98% of which are MSM). All participants in the *Engage Cohort* and *l'Actuel PrEP Cohort* provided written informed consent prior to data collection.

Table 5.2.1. Summary of key PrEP-related model population characteristics, parameters, and calibration outcomes.

Model population characteristic	Percentage (90%CrI)	Source

Percentage of MSM not living with HIV eligible for PrEP on January 1, 2013*	57.6% (56.0%-59.1%)	Model estimate
Percentage of MSM not living with HIV eligible for PrEP on January 1, 2013 by sexual activity group*	Low: 30.5% (28.2%-33.2%) Medium: 61.5% (59.0%-64.1%) High: 89.0% (89.1%-88.8%)	Model estimate
Proportion of MSM not living with HIV eligible for PrEP on January 1, 2013 by age group*	15-24 years: 43.7% (41.9%-45.3%) 25-54 years: 66.8% (65.7%-68.6%) 55+ years: 48.3% (45.4%-49.8%)	Model estimate
Parameter	**Value or prior distribution**	**Source**
PrEP effectiveness (assuming the same adherence levels as the source)	86%	Molina et al. [6]
Probability of PrEP uptake among MSM eligible for PrEP by year*	2013-2014: ~U(0, 0.01) 2015: ~U(0.01, 0.24) 2016: ~U(0.01, 0.17) 2017: ~U(0.01, 0.26) 2018: ~U(0.06, 0.32) 2019-2022: ~U(0.06, 0.32)	Calibration (informed by the *Engage Cohort*[30])
PrEP discontinuation rate (months^{-1})†	~U$\left(\frac{1}{13.00}, \frac{1}{8.44}\right)$	Calibration (informed by *l'Actuel PrEP Cohort*[31])
Frequency of HIV testing while on PrEP (months)	One month post-initiation and every subsequent three months	Québec PrEP guidelines[16, 17]
Calibration outcomes	**Year(s)**	**Source**
Prevalence of lifetime PrEP use among all MSM by year	2017-2019	*Engage Cohort*[30]
PrEP coverage (i.e., current use) among MSM not living with HIV by year	2017-2019	*Engage Cohort*[30]

Abbreviations: Pre-exposure prophylaxis (PrEP); credible interval (CrI); men who have sex with men (MSM).

*In the model, MSM not living with HIV were eligible for PrEP if they had any anal sex acts unprotected by condoms in the past six months and either: 1) ≥2 partnerships in the past six months or 2) ≥2 lifetime uses of post-exposure prophylaxis.
†The PrEP discontinuation rate was converted to a probability for use in a Bernoulli distribution.

PrEP parameterization

The PrEP module required effectiveness, uptake, and discontinuation parameters (Table 5.2.1). To parameterize effectiveness, we reviewed published literature and selected the IPERGAY trial's intention-to-treat estimate of 86%, considering its relevance to Québec and accounting for imperfect PrEP adherence. We estimated the remaining parameters by calibrating to *Engage* data on lifetime PrEP use among all MSM and PrEP coverage among those not living with HIV.

We calibrated annual probabilities of PrEP uptake among PrEP-eligible men with prior distributions informed by *Engage*. *Engage* captured self-reported information on the year of first PrEP use among participants who reported ever using PrEP at baseline and using PrEP in the past six months during follow-up visits. We estimated the proportion of PrEP-eligible men that first took PrEP each year, accounting for the complex survey design using RDS-II sampling weights[32] and for loss-to-follow-up using inverse probability of censoring weights (Figure 5.3.1Figure 5.3.2). To obtain estimates before 2017, we assumed the number eligible at baseline was constant. For calibration, we considered the 95%CI bounds and made additional assumptions. First, since no participant reported starting PrEP in 2013 and only seven reported starting in 2014, we assumed uptake was equivalent in those years and informed the prior by the 95%CI of the 2014 estimate. Second, there was increased uncertainty regarding attrition and measurement of PrEP initiation at the last study visit, possibly impacting the estimate for 2019. Since the 95%CI of the 2018 estimate was wide and included plausible values for both years, we used this to inform the prior distribution of the uptake probability in 2019. Finally, we incorporated additional uncertainty in all uptake probability prior distributions to allow for any residual bias due to attrition (Table 5.2.1).

Clinical data from l'*Actuel* informed the PrEP discontinuation rate prior distribution. We defined PrEP discontinuation based on three criteria: 1) reported stopping at a follow-up visit, 2) absence of reported stopping but undergoing another PrEP consultation, or 3) >180 days between visits. The discontinuation date was determined by the available data, as follows: 1) the reported stop date, 2) the date of the visit where stopping was reported, or 3) 3-6 months (randomly chosen from a uniform distribution) after the last visit before stopping. PrEP retention (i.e., duration of continuous use) was calculated as the time between initiation and discontinuation. The prior bounds of the discontinuation rate were obtained by inverting the age-standardized interquartile range of individual retention (Table 5.2.1).

Modelling of PrEP initiation and discontinuation

Starting from 2013, the model simulated oral PrEP use. Matching the Québec PrEP guidelines, men susceptible to HIV acquisition were eligible for PrEP if they had any anal sex acts unprotected by condoms in the past six months and either: 1) ≥2 partnerships in the past six months or 2) ≥2 lifetime PEP uses[16, 17].

At each time step, a Bernoulli distribution using the calibrated uptake probabilities determined if each eligible man would initiate PrEP. Those selected for PrEP underwent HIV testing and started PrEP if the result was negative. HIV testing while on PrEP occurred after the first month of use and every subsequent three months. Those who tested positive for HIV immediately discontinued PrEP and were linked to care.

Finally, the calibrated discontinuation rate was converted to a probability and used in a Bernoulli distribution to determine which PrEP users would discontinue at each time step.

Impacts of COVID-19 pandemic disruptions on sexual behaviours and PrEP

The COVID-19 pandemic's impact was incorporated into the model starting from March 2020. Sexual activity, prevention, and treatment changes were informed by *Engage* data. PrEP use changes were also informed by *l'Actuel*. From March to June 2020, partner change rates decreased, with a 0.5 and 0.2 absolute reduction in the mean number of annual partners for those living and not living with HIV, respectively, in the low-medium sexual activity group and 5.0 and 10.4 for those living and not living with HIV, respectively, in

the high sexual activity group. Due to service disruptions, reductions in the probabilities of testing annually (by 51% and 21% in the low-medium and high sexual activity groups, respectively), PEP initiation (by 43%), PrEP initiation (by 35%), and PrEP retention (discontinuation probability increased by 153%) remained until July 2021. After this time, we assumed a return to pre-pandemic levels.

Model outputs and impact evaluation measures

We tracked characteristics of PrEP use and coverage (percentage of susceptible individuals taking PrEP) and HIV acquisitions over time. We then calculated the annual and cumulative numbers of HIV acquisitions. Finally, we estimated the annual incidence risk by the number of HIV acquisitions each year divided by the number susceptible to HIV acquisition at year-start.

The HIV epidemic was simulated ten times for each of the 100 calibrated parameter sets and the outputs were summarized by the mean. We performed this process under two scenarios: the provincial PrEP intervention scenario and the counterfactual scenario without PrEP. We measured PrEP's population-level impact by the fraction of HIV acquisitions averted by PrEP over the total number of acquisitions in the counterfactual scenario without PrEP.

Sensitivity analyses

In sensitivity analyses, we relaxed the eligibility criteria since MSM may have received PrEP despite not meeting all the provincial criteria[33]. We considered two scenarios, each applying only one eligibility criterion at a time: 1) condomless anal sex in the past six months, and 2) ≥2 partnerships in the past six months. The PrEP uptake rates were kept as calibrated.

Additionally, we assessed the robustness of our results to the assumed PrEP effectiveness, increasing it to 96%, as data indicated high adherence among continuous users (supplementary materials).

Alternative PrEP intervention scenarios

We simulated alternative, hypothetical intervention scenarios to explore how PrEP's impact could have been optimized (Table 5.2.2). These involved assessing the potential impact of PrEP prioritization (either to men in the high sexual activity group or those aged ≤45 years), increased coverage levels (up to a maximum of 30% by 2019, approximating the coverage reached in Vancouver, where PrEP is free for eligible individuals), and increased retention (reducing the discontinuation probability by 25% and 50%).

Table 5.2.2. Pre-exposure prophylaxis (PrEP) intervention scenarios modelled among men who have sex with men in Montréal over 2013-2021.

Scenario	PrEP eligibility criteria	PrEP Usage
Provincial PrEP intervention scenario		
Provincial PrEP intervention	Provincial criteria*	Applied calibrated uptake rates
Alternative PrEP intervention scenarios		
Prioritized use	High sexual activity group	Matched the coverage of the provincial intervention scenario over time
Prioritized use	Aged ≤45 years	Matched the coverage of the provincial intervention scenario over time
Increased coverage	Provincial criteria*	Matched coverage targets of 5% or 10% by 2015 and 20% or 30% by 2019†
Increased coverage + prioritized use	High sexual activity group	Matched coverage targets of 5% or 10% by 2015 and 20% or 30% by 2019†
Increased coverage + prioritized use	Aged ≤45 years	Matched coverage targets of 5% or 10% by 2015 and 20% or 30% by 2019†
Increased retention (probability of discontinuation reduced by 25% and 50%)	Provincial criteria*	Applied calibrated uptake rates

Abbreviations: Pre-exposure prophylaxis (PrEP)

*In the model, MSM not living with HIV were eligible for PrEP if they had any anal sex acts unprotected by condoms in the past six months and either: 1) ≥2 partnerships in the past six months or 2) ≥2 lifetime uses of post-exposure prophylaxis.

[†]Starting with 0% coverage in 2013 and using linear interpolation to set the targeted coverage between 2013-2015 and 2015-2019. The 2019 coverage target was then maintained through to the end of 2021.

Ethics

The *McGill University Research Ethics Board* and the *Research Institute of the McGill University Health Centre* approved this study.

Results

PrEP coverage

According to *Engage* data, PrEP uptake was low after Québec's interim guidelines were published in 2013 and gradually started increasing in 2015, and reaching 5% (95%CI: 3%-7%) coverage among MSM not living with HIV by 2018 (Figure 5.2.1). In 2020, *Engage* data indicated 10% (95%CI: 6%-16%) of Montréal MSM not living with HIV were currently on PrEP. Our model reflected these trends well, matching the estimated PrEP coverage in MSM not living with HIV at 4% (90% credible interval [CrI]: 2%-6%) in 2018 and 10% (90%CrI: 8%-12%) in 2020 (Figure 5.2.1). Among the PrEP-eligible population, which accounted for 62% (90%CrI: 61%-64%) of MSM not living with HIV (Figure 5.3.5), current use reached 16% (90%CrI: 13%-19%) in 2020 (Figure 5.3.6). During the initial waves of the COVID-19 pandemic, there was a significant decline in PrEP coverage due to reduced initiation and increased discontinuation (by model design), but coverage rebounded in mid-2021 (Figure 5.2.1). Throughout the study period, PrEP usage varied across different age and sexual activity groups (Figure 5.2.1).

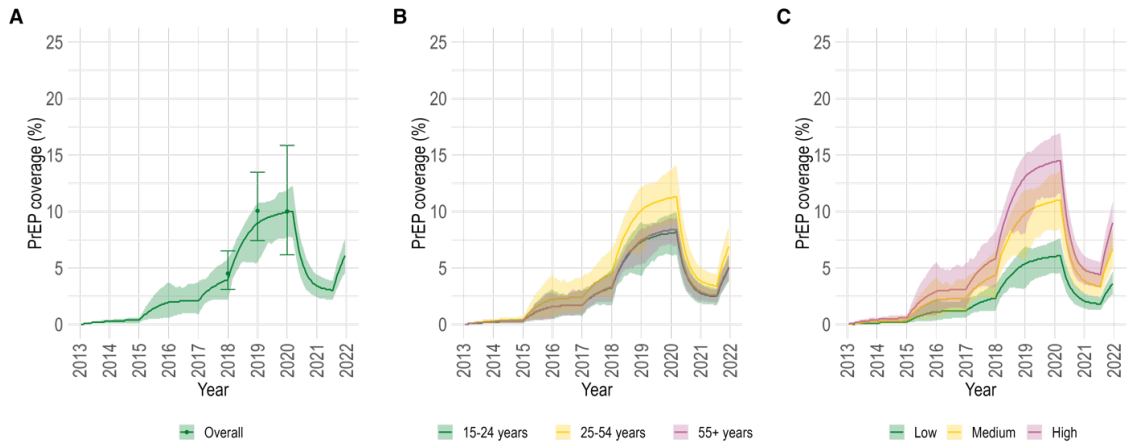

Figure 5.2.1. Pre-exposure prophylaxis (PrEP) coverage among men who have sex with men (MSM) not living with HIV in Montréal

Estimated PrEP coverage over 2013-2021 among MSM not living with HIV in Montréal: overall (panel A) and stratified by age (panel B) and sexual activity group (panel C). The coloured lines and bands show the model posterior mean and 90% credible intervals, respectively. The three points and bars in panel A display the estimated PrEP coverage and 95% confidence intervals calculated from *Engage* and adjusted by RDS-II and inverse probability of censoring weights.

Annual HIV incidence

The modelled annual HIV incidence was 0.4 per 100 person-years (90%CrI: 0.3-0.6) in 2013 and decreased to 0.2 per 100 person-years (90%CrI: 0.1-0.2) in 2021 (Figure 5.2.2). Prior to PrEP scale-up, the estimated annual incidence differed markedly by age and sexual activity levels (Figure 5.2.2). In 2013, the oldest age group (55+) had the lowest estimated annual incidence (0.2 per 100 person-years [90%CrI: 0.1-0.3]) compared to the 15-24-year-olds (0.3 per 100 person-years [90%CrI: 0.2-0.5]) and the 25-54-year-olds (0.5 per 100 person-years [90%CrI: 0.3-0.7]). By the end of 2020, incidence reached 0.1 per 100 person-years in the 15-24 (90%CrI: 0.1-0.2) and 55+ (90%CrI: 0-0.1) age groups, and 0.2 per 100 person-years (90%CrI: 0.1-0.3) in those aged 25-54. Across sexual activity levels, those with more sexual partners had a higher incidence. Over time, the most pronounced incidence reductions were exhibited by the highest sexual activity group, decreasing from 0.8 per 100 person-years (90%CrI: 0.6-1.1) in 2013 to 0.3 per 100 person-years (90%CrI: 0.2-0.5) in 2021. Considering PrEP use status over 2016-2021, incidence was higher

among MSM eligible but not taking PrEP and even higher among those who discontinued PrEP (Figure 5.2.3).

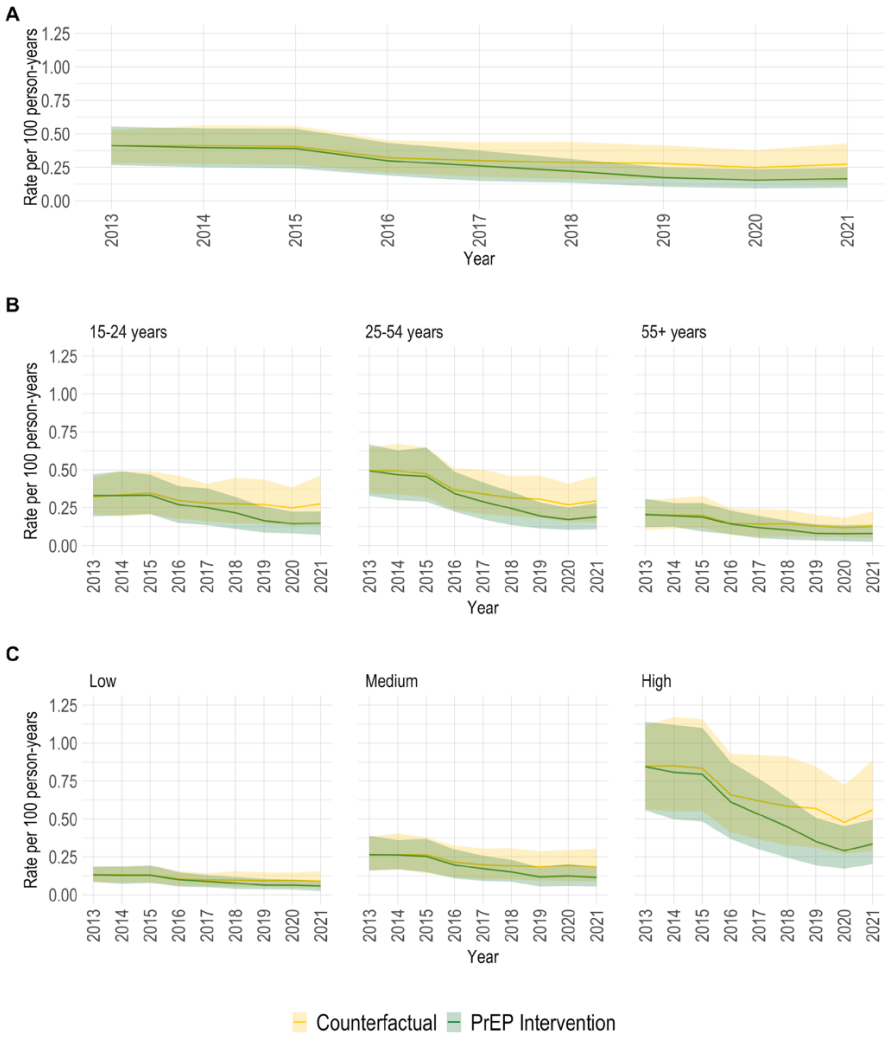

Figure 5.2.2. Annual HIV incidence in the provincial pre-exposure prophylaxis (PrEP) intervention and counterfactual scenarios.

Estimated HIV incidence rates over 2013-2021 among men who have sex with men (MSM) in Montréal under the provincial pre-exposure prophylaxis (PrEP) intervention and counterfactual scenarios. The rates are presented overall (panel A) and stratified by age (panel B) and sexual activity group (panel C). The coloured lines and bands show the posterior mean and 95% credible intervals, respectively.

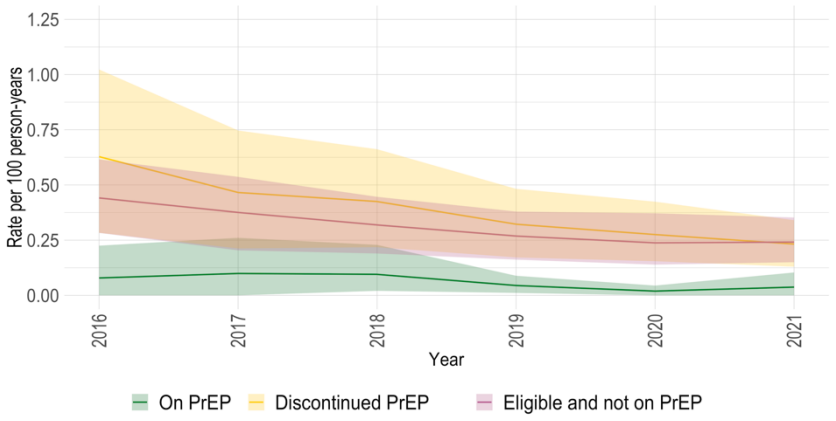

Figure 5.2.3. Annual HIV incidence by pre-exposure (PrEP) use status in the provincial PrEP intervention scenario.
Estimated HIV incidence rates under the provincial pre-exposure prophylaxis (PrEP) intervention scenario over 2013-2021 among men who have sex with men (MSM) in Montréal, stratified by PrEP use status. The coloured lines and bands show the posterior mean and 95% credible intervals, respectively.

Impact evaluation

Over the study period, the annual fractions of HIV acquisitions averted by PrEP increased (Figure 5.2.4). In the early years of PrEP availability, when coverage was lowest, it had a limited impact on averting HIV acquisitions. However, starting in 2017, PrEP began to have greater impacts. In 2021, PrEP averted an estimated 38% (90%CrI: 20%-53%) of HIV acquisitions. Given the low coverage before 2015, we focused the cumulative evaluation from 2015 onward and estimated that PrEP averted 20% (90%CrI: 11%-30%) of HIV acquisitions from 2015 to 2022 (Figure 5.2.4).

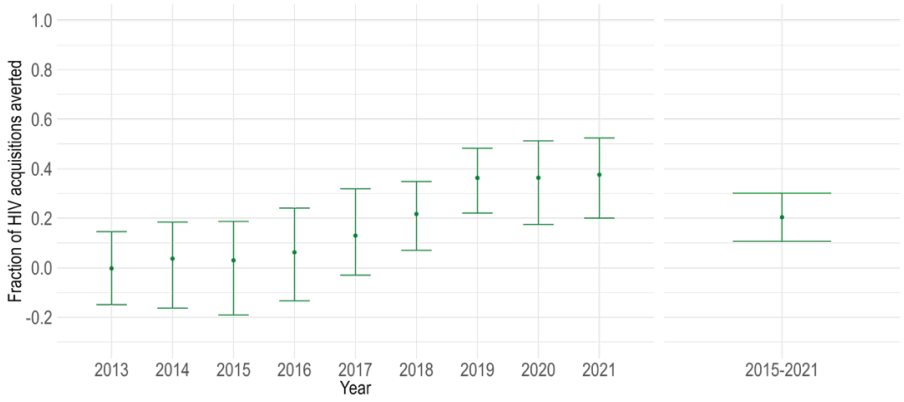

Figure 5.2.4. HIV Acquisitions averted under the provincial pre-exposure prophylaxis (PrEP) intervention scenario.
Estimated annual (2013-2021) and cumulative (2015-2021) fractions of acquisitions averted due to the provincial PrEP intervention among men who have sex with men in Montréal. The coloured points and bars show the posterior mean and 90% credible intervals, respectively.

Sensitivity Analyses

Our estimation of HIV incidence under PrEP intervention was not sensitive to the level of PrEP efficacy (86% vs 96%) or loosened eligibility criteria (Figure 5.3.7).

Alternative PrEP intervention scenarios

Our alternative (hypothetical) analyses (Table 5.2.2) suggested that to have improved the impact of PrEP compared to the provincial intervention scenario, prioritizing MSM in the high sexual activity group (same overall coverage) or attaining higher overall PrEP coverage of 5% or 10% and 20% or 30% coverage by 2015 and 2019, respectively, would have been needed (Figure 5.2.5). Prioritizing PrEP to MSM in the high sexual activity group (same coverage as the provincial intervention) cumulatively averted 30% (90%CrI: 19%-42%) of HIV acquisitions over 2015-2021, with a peak annual fraction averted of 52% (90%CrI: 30%-69%) in 2021 (Figure 5.2.5). Even higher impacts could have resulted by reaching coverage targets of 5% or 10% by 2015 and 20% or 30% by 2019, especially when combined with prioritized use for MSM with high sexual activity levels. For instance, the scenario with the smallest increase in PrEP coverage, reaching targets of 5% in 2015 and 20% in 2019, averted 49% (90%CrI: 39%-57%) of HIV acquisitions between 2015-2022 (under provincial eligibility criteria), and up to 68% (90%CrI: 54%-70%) when

prioritizing PrEP to the high sexual activity group. Conversely, the scenario with the largest increase in PrEP coverage, mirroring the coverage in Vancouver, reached targets of 10% by 2015 and 30% by 2019 and, under provincial eligibility criteria, averted 63% (90%CrI: 54%-70%) of HIV acquisitions over 2015-2021.

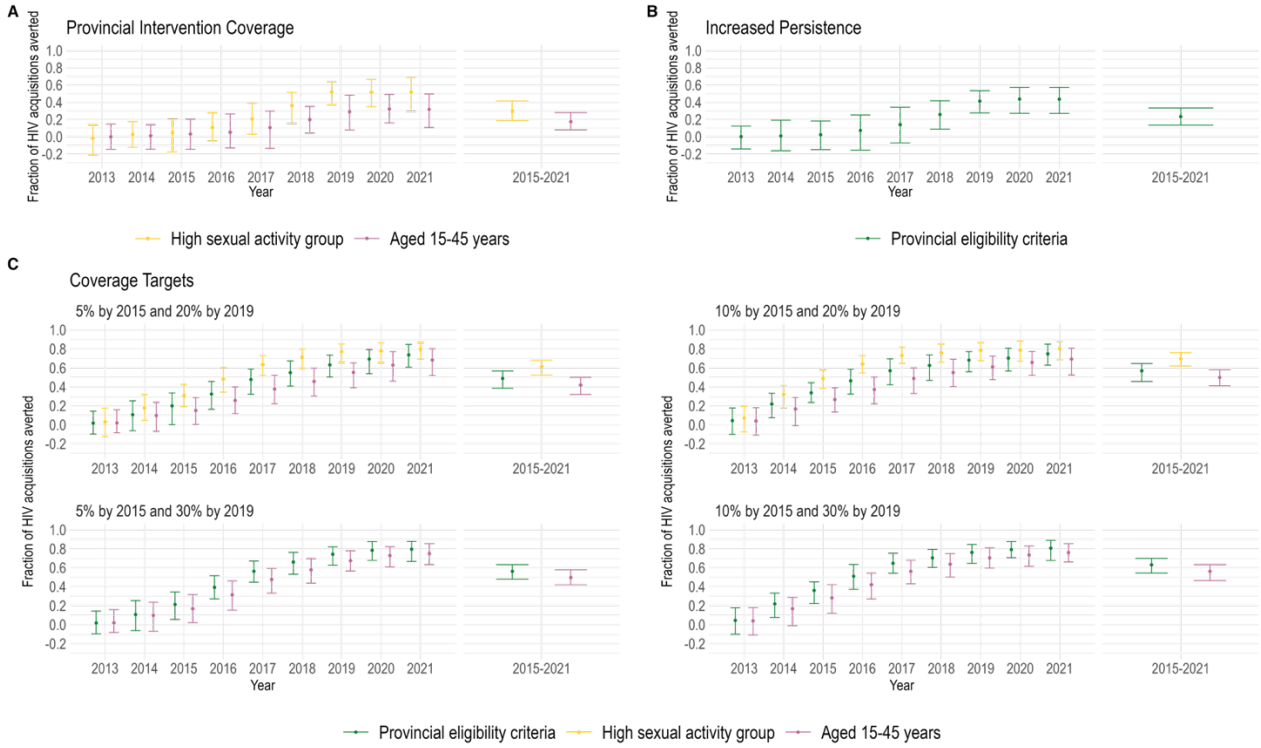

Figure 5.2.5. HIV Acquisitions Averted in Alternative Intervention Scenarios.
Estimated fraction of acquisitions averted due to pre-exposure prophylaxis (PrEP) intervention among men who have sex with men (MSM) in Montréal under alternative (hypothetical) intervention scenarios. For each, the annual estimates from 2013-2021 and cumulative estimate over 2015-2021 are shown. The coloured points and bars show the posterior mean and 95% credible intervals, respectively. The panels display the results of: A) maintaining the observed PrEP coverage but prioritizing uptake in 1) the high sexual activity group or 2) those aged 15-45 years; B) maintaining the calibrated PrEP uptake probabilities but increasing retention on PrEP (for simplicity, only the results of the 50% decrease in discontinuation probability scenario are plotted); and C) increasing coverage up to a maximum of 30% by 2019 for three different uptake assumptions: 1) the same as the provincial PrEP eligibility criteria, or prioritizing uptake in 2) the high sexual activity group or 3) those aged 15-45 years. Note in the scenarios prioritizing MSM in the high

sexual activity group it was not possible to reach 30% coverage by 2019 due to the insufficient number of individuals in the group. The results for these scenarios are not presented.

Discussion

This study presents a population-level estimate of PrEP's impact, considering both direct and indirect effects. Using a detailed agent-based model of sexual HIV transmission and prevention among Montréal's MSM, we created a valid counterfactual scenario without PrEP and found that, despite relatively low coverage, PrEP may have averted 20% (90%CrI: 11%-30%) of new HIV acquisitions between 2015-2022 in this population. From 2015-2019, as time and coverage accrued to 10% of MSM not living with HIV and 16% of the PrEP-eligible, the annual fraction of acquisitions averted by PrEP rose from 3% to 36%. Afterward, despite the COVID-19 pandemic disruptions to coverage, this level of impact persisted due to the transmission chains already prevented by PrEP.

Although our analysis suggests considerable population-level benefits of PrEP intervention among MSM in Montréal, it also highlights missed prevention opportunities. One obvious way to improve PrEP's impact is to attain higher coverage. At the observed levels, prioritizing MSM with higher sexual activity levels might have improved impact, but not to the same extent as achieving higher coverage with the current provincial eligibility criteria, which approximately 60% of MSM not living with HIV met in our model. Increasing coverage to 5% or 10% in 2015 and 20% or 30% in 2019 could have prevented more than twice the number of HIV acquisitions since 2015. Given the coverage estimates over 2017-2020 for Vancouver MSM, we believe that levels of 10% in 2015 and 30% in 2019 could have been feasible in Montréal and would have averted an estimated 63% (90%CrI: 54%-70%) of HIV acquisitions would have been averted instead of 20%. Vancouver's higher coverage has been attributed to total public funding for PrEP in that province[34], whereas the PrEP co-payment in Québec can be as high as CAD$96.74 per month[18]. Even matching 5% coverage in 2015 and 20% in 2019 could have averted 49% (90%CrI: 39%-57%) of HIV acquisitions between 2015-2022, rising to 68% (90%CrI: 54%-70%) if efforts focused on MSM frequently engaging in anal sex with different partners.

Two other studies have examined the impact of PrEP intervention empirically using surveillance data and observed changes HIV diagnoses pre- and post-PrEP implementation[11, 12]. In Australia's state of New South Wales, PrEP reached an estimated 20% of MSM living without HIV in 2016 and reduced new diagnoses of recent HIV acquisitions among MSM by 31.5% (95%CI: 11.3%-47.3%) in a 12-month post-implementation period, compared to the year prior[11]. A similar study in Scotland, where PrEP is free-of-cost from national clinics, estimated that 20% of MSM attending such clinics were prescribed PrEP and showed a 35.6% (95%CI: 7.1%-55.4%) reduction in new diagnoses of recent HIV acquisitions among MSM over a 24-month post-implementation period[12].

It is challenging to directly compare these findings to ours due to different time frames (PrEP's impact is expected to accrue over time) and variations in coverage and use. The most comparable period of our study is over 2017 and 2018 when coverage was beginning to rise. In those years, we estimated that 13% (90%CrI: 0%-32%) and 22% (90%CrI: 7%-35%) of acquisitions were averted, respectively. While differences between our estimates may stem from lower coverage in our study, heterogeneity in risk across the populations could also differ. Additionally, other factors like changes in HIV testing trends, the use of diagnoses of recent acquisitions to proxy incidence, and concomitant improvements in the treatment and care cascade could influence the findings of these studies.

Our analysis helped highlight missed opportunities in PrEP delivery in the city. For example, it took approximately two years for PrEP coverage to start increasing after Québec issued guidelines. Better awareness of PrEP's efficacy and safety among healthcare providers and potential users following the early cessation of the IPERGAY trial in 2014 could have encouraged earlier use. Even after PrEP expanded, coverage maximized at 10%, never reaching the Vancouver's levels. Our model indicated that many eligible MSM were not engaged in PrEP care yet could have benefited from its use, as evidenced by their higher HIV incidence. The financial burden of PrEP in Montréal remains an important barrier, potentially leaving behind those most at risk of HIV acquisition[35].

The findings from our impact evaluation should be interpreted cautiously. Our model used simplifying assumptions about disease progression, HIV transmission, and prevention use. For instance, individuals on PrEP may be less likely to serosort (i.e., choose partners not living with HIV), and PLHIV may preferentially mix with PrEP users[30, 36]. If mixing was less assortative by HIV status among those on PrEP, we might have slightly overestimated the impact of PrEP. However, this potential bias should be small given the high viral suppression levels. Additionally, the model did not consider risk compensation or changes in sexual behavior that could be associated with PrEP use, which could overestimate the impact of PrEP. However, this overestimation should be small, given PrEP's effect size. Finally, the model did not differentiate between daily and on-demand regimens, given their equivalent efficacy under perfect adherence.

Our analysis has several strengths. Firstly, we leveraged data from multiple cohorts and surveys of MSM in Montréal to parameterize and calibrate the model. Secondly, using a model allowed us to construct an appropriate counterfactual scenario without a suitable control group[13]. Thirdly, we controlled for changes in Québec's treatment eligibility criteria. Lastly, our impact estimates include PrEP's direct effects in preventing HIV acquisition among users and the indirect benefits to MSM not on PrEP due to overall decreases in HIV prevalence.

Conclusions

PrEP has the potential to contribute significantly to HIV elimination as a key part of combination HIV prevention. However, global scale-up has been slow, resulting in sub-optimal coverage and limited impact on incidence reductions[37]. In Montréal, despite modest coverage, PrEP had a notable impact on HIV transmission, complementing declining incidence and high ART coverage. Free PrEP could remove important barriers, but more needs to be done to address stigma, discrimination, and certain physicians' reticence to prescribe PrEP, amongst others[38-41]. The availability of alternative formulations like long-acting injectable PrEP could further usage and support adherence. By removing barriers, we can accelerate HIV elimination among MSM and other vulnerable populations.

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5.3. Manuscript 2: Supplementary Materials

5.3.1. Appendix 1

Pre-exposure prophylaxis (PrEP) parameterization: Additional details

Eligibility

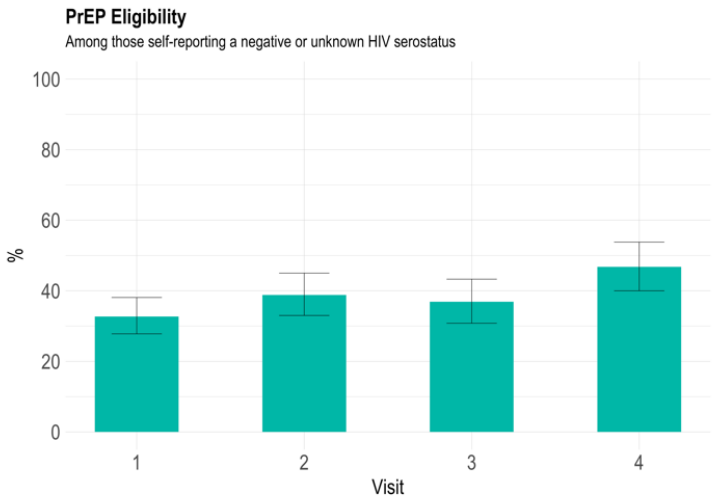


Figure 5.3.1. Empirical estimates of pre-exposure prophylaxis (PrEP) eligibility among men who have sex with men (MSM) in Montréal.
The estimated annual percentage of Montréal MSM eligible for PrEP (according to the modelled provincial criteria) among Engage participants that self-reported a negative or unknown HIV serostatus. The first four Engage study visits occurred annually over 2017-2021. All estimates were adjusted by RDS-II and inverse probability of censoring weights. The error bars show the estimated 95% confidence intervals.

Initiation

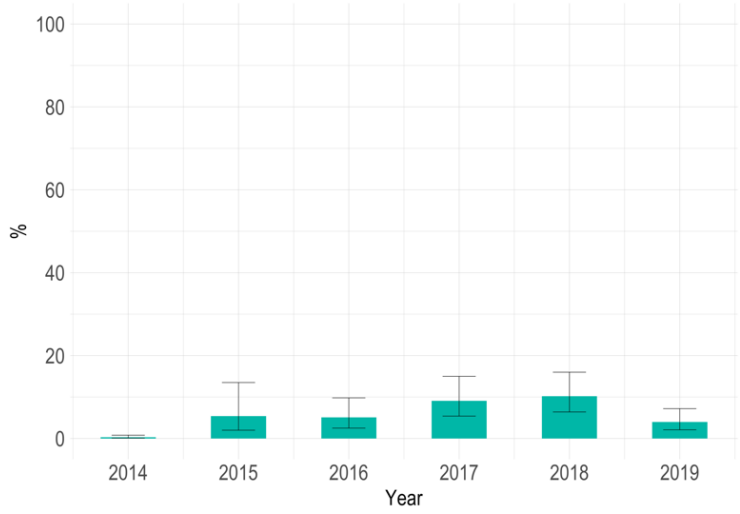
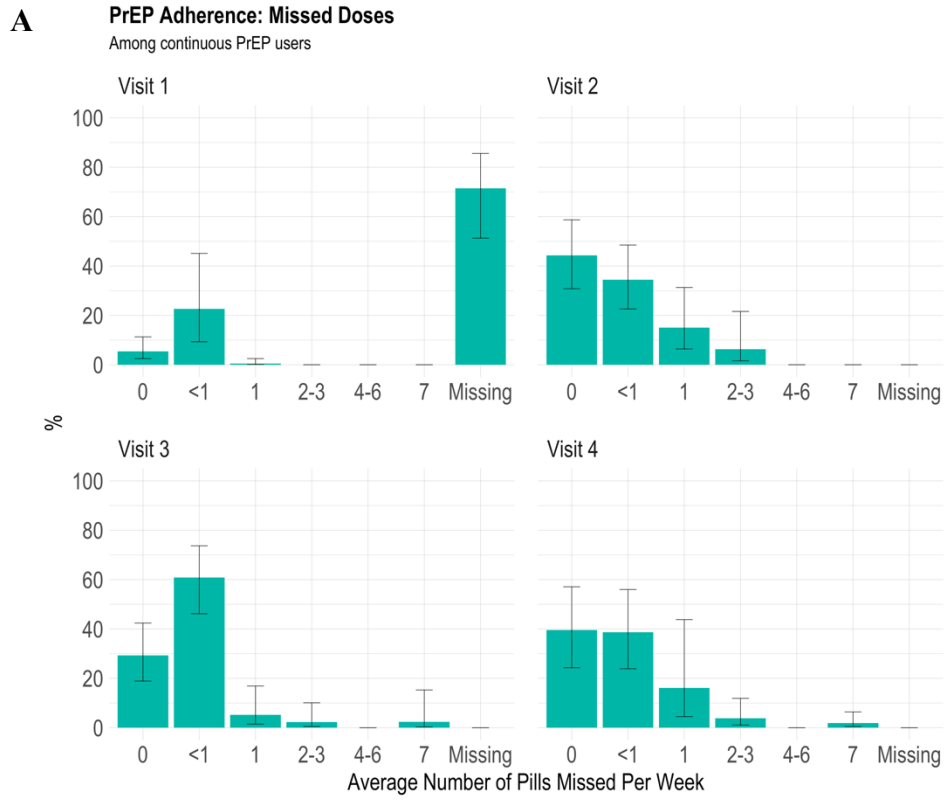


Figure 5.3.2. Empirical estimates of pre-exposure prophylaxis (PrEP) uptake among men who have sex with men (MSM) in Montréal.
The estimated percentage of Montréal MSM that reported first taking PrEP in a given year among Engage participants eligible for PrEP (according to the modelled provincial criteria). No Engage participant reported first taking PrEP in 2013. To obtain estimates before 2017 (when the Engage cohort study began), we assumed the number eligible at baseline was constant. All estimates were adjusted by RDS-II and inverse probability of censoring weights. The error bars show the estimated 95% confidence intervals.

Adherence

Engage measured adherence among continuous PrEP users (those reporting ever using PrEP continuously at baseline or in the past six months throughout follow-up) at all visits by capturing the self-reported number of daily doses missed per week (*"On average, how many days per week have you missed your dose of PrEP medication?"*). Additionally, a measure of PrEP-protected anal sex was included in the study questionnaire as of the third visit (*"In the past 6 months, how often were you on PrEP when you had sexual activities involving anal sex (either as top or bottom)?"*). Together, these measures indicated consistently high levels of self-reported adherence among MSM taking PrEP daily (Figure 5.3.3). However, across visits, approximately 40%-60% of Engage participants reporting PrEP use self-reported strictly continuous use (Figure 5.3.4). Therefore, many Montréal MSM do indeed use PrEP on a situational basis. Without understanding the adherence or

pill taking frequency of on-demand users in our setting, we did not model differential PrEP adherence. Instead, we parameterized PrEP effectiveness by the intention-to-treat estimate from the IPERGAY trial (which included Montréal MSM) [1]. Among all IPERGAY participants, 43% (95%CI: 35%-51%) self-reported correct use of the on-demand PrEP schedule[1]. In sensitivity analyses, we modelled an increased efficacy of 96%, corresponding to taking four doses per week, the threshold often used to define high adherence[2, 3].



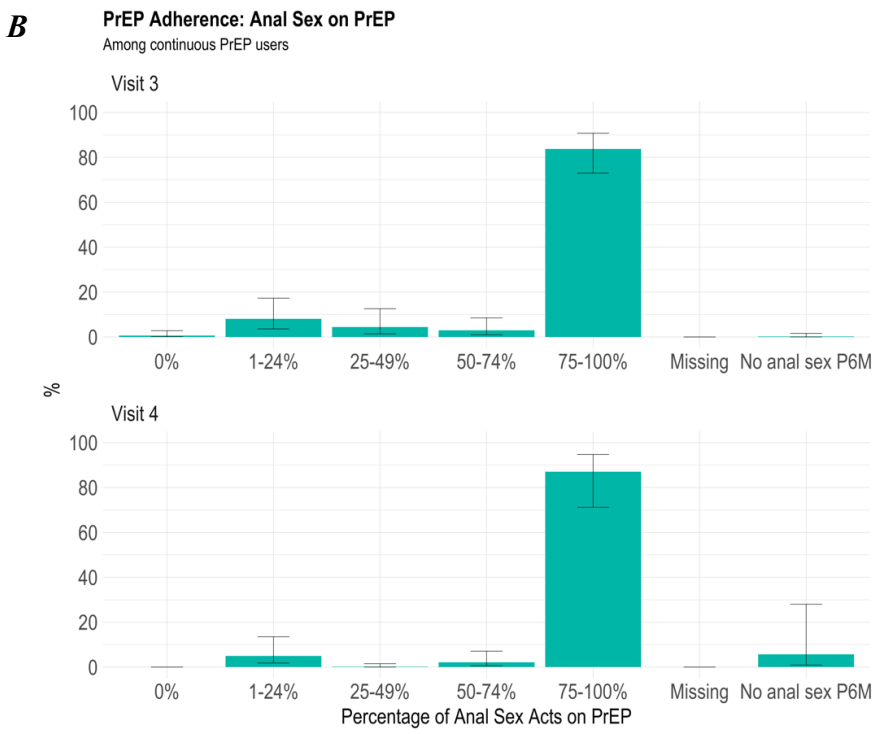


Figure 5.3.3. Empirical estimates of pre-exposure prophylaxis (PrEP) adherence among men who have sex with men (MSM) in Montréal.

Estimates of PrEP adherence among Montréal MSM calculated using the Engage cohort and adjusted by RDS-II and inverse probability of censoring weights. The first four Engage study visits occurred annually over 2017-2021. Panel A displays the self-reported average number of pills missed per week among continuous PrEP users at each study visit. Panel B displays the self-reported percentage of anal sex acts covered by PrEP among continuous PrEP users at the third and fourth study visits. The error bars show the estimated 95% confidence intervals.

Schedule

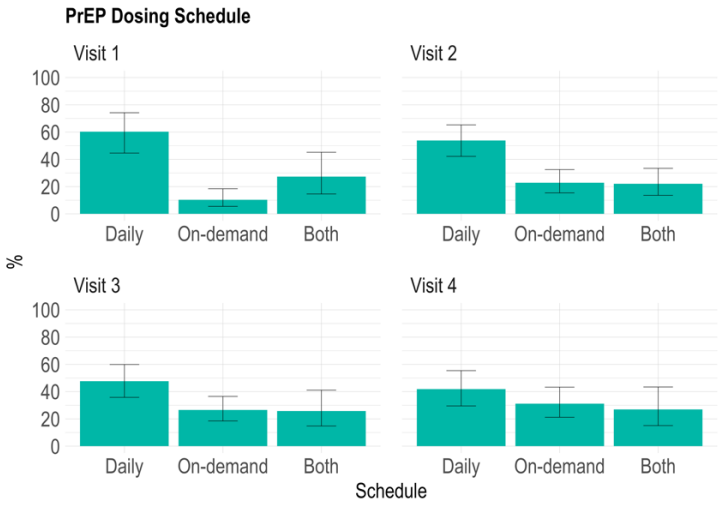


Figure 5.3.4. Empirical estimates of pre-exposure prophylaxis (PrEP) dosing schedule among men who have sex with men (MSM) in Montréal.
The estimated percentage of PrEP users following a daily or on-demand dose schedule calculated using the Engage cohort and adjusted by RDS-II and inverse probability of censoring weights. The error bars show the estimated 95% confidence intervals. The first four Engage study visits occurred annually over 2017-2021.

5.3.2. Appendix 2

Additional Model Results

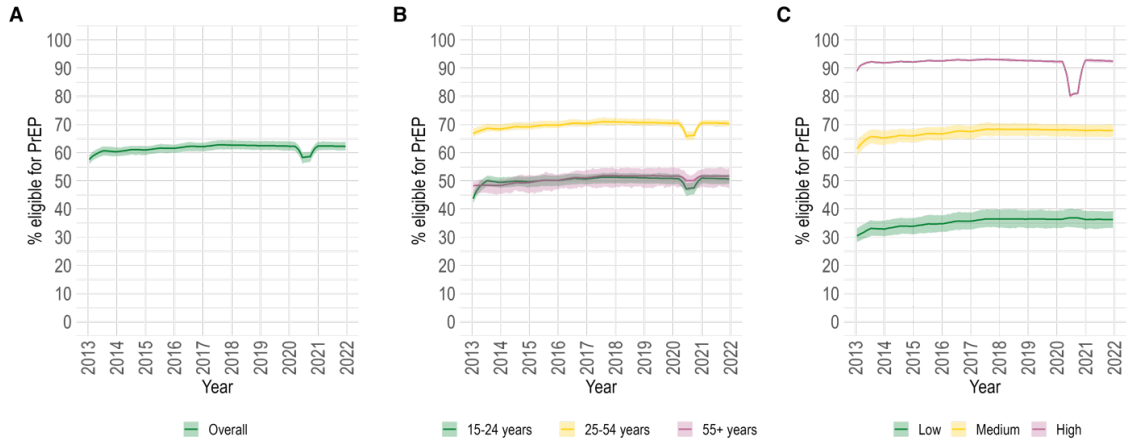


Figure 5.3.5. Modelled pre-exposure prophylaxis (PrEP) eligibility among men who have sex with men (MSM) not living with HIV in Montréal.
The model estimated percentage of MSM not living with HIV eligible for PrEP over 2013-2021 in Montréal: overall (panel A) and stratified by age (panel B) and sexual activity group (panel C). The coloured lines and bands show the model posterior mean and 90% credible intervals, respectively.

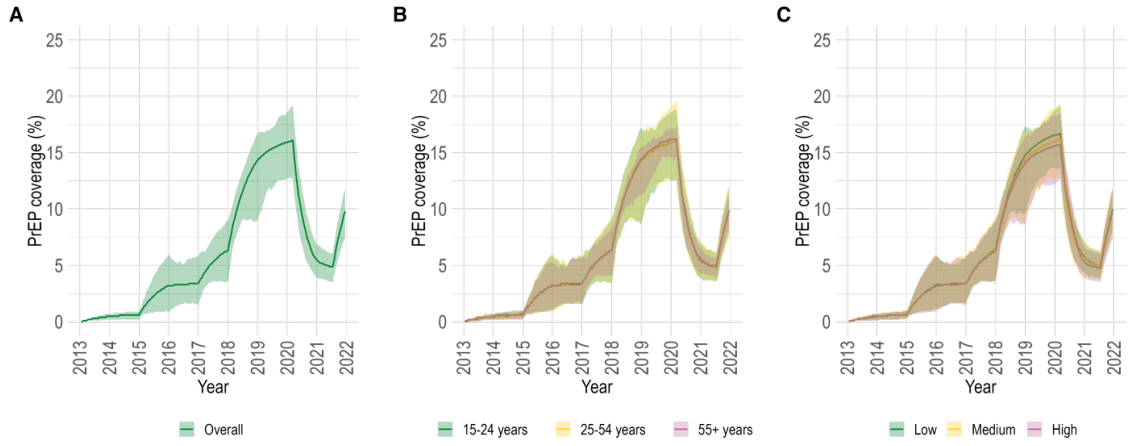


Figure 5.3.6. Modelled pre-exposure prophylaxis (PrEP) coverage among PrEP-eligible men who have sex with men (MSM) not living with HIV in Montréal.
The model estimated PrEP coverage over 2013-2021 among MSM eligible for PrEP in Montréal: overall (panel A) and stratified by age (panel B) and sexual activity group (panel

C). The coloured lines and bands show the model posterior mean and 90% credible intervals, respectively.

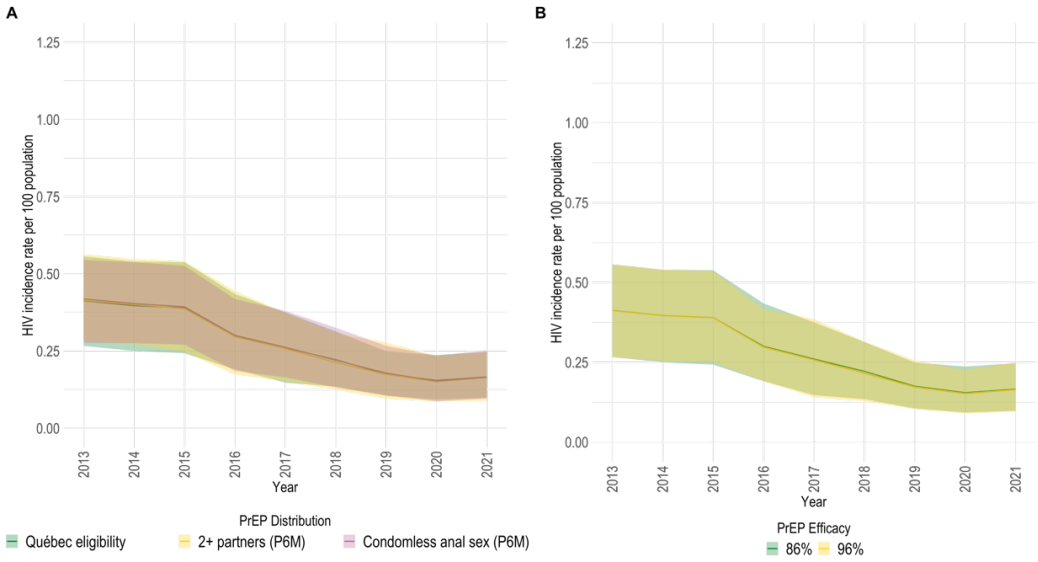


Figure 5.3.7. Sensitivity Analyses.
The model estimated HIV incidence rates over 2013-2021 among Montréal men who have sex with men (MSM) under the provincial pre-exposure prophylaxis (PrEP) intervention scenario with different PrEP-eligibility criteria (panel A) and with different PrEP efficacies (Panel B). The coloured lines and bands show the posterior median and 90% credible intervals, respectively.

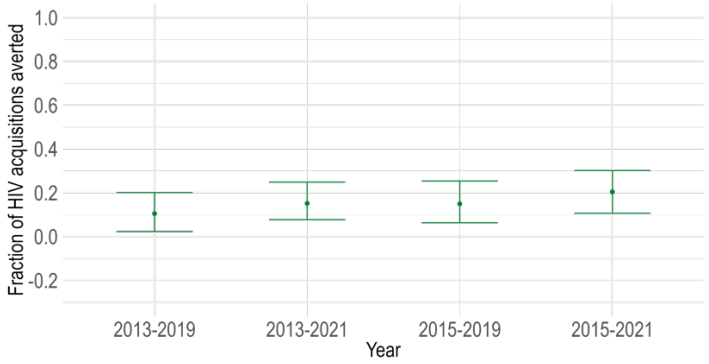


Figure 5.3.8. Cumulative Acquisitions Averted.
Estimated cumulative fraction of acquisitions averted due to pre-exposure prophylaxis (PrEP) intervention among men who have sex with men (MSM) in Montréal (provincial PrEP intervention scenario) over varying time periods. The coloured points and bars show the posterior mean and 90% credible intervals, respectively.

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Chapter 6. Manuscript 3

6.1. Preface to Manuscript 3

The two previous manuscripts examined combination HIV prevention and the population-level impact of PrEP on HIV acquisition in Montréal. In an elimination context, developing the tools to annually monitor HIV incidence and epidemic metrics could enable decision-makers to track their response and refocus efforts accordingly. Such tools must be both robust in estimating multiple epidemic metrics and able to triangulate different data sources, including routinely available surveillance data. While PHAC has tools for monitoring HIV epidemics in Canada, the publicly available results typically do not include provincial or municipal estimates for key populations such as gbMSM and PWID. In Manuscript 3, I developed a mathematical model that uses provincial surveillance data from the INSPQ. In this chapter, I provide estimates of HIV incidence, HIV prevalence, the undiagnosed fraction, the fraction diagnosed that took ART, and the median time to diagnosis for MSM and PWID in Montréal and across Québec. This article was published in the *Journal of the International AIDS Society* in September 2022[140].

6.2. Manuscript 3: Measuring progress towards reaching zero new HIV acquisitions among key populations in Québec (Canada) using routine surveillance data: a mathematical modeling study

Carla M Doyle[1], Joseph Cox[1,2,3], Rachael M Milwid[1], Raphaël Bitera[4], Charlotte Lanièce Delaunay[1,3], Michel Alary[4,5,6], Gilles Lambert[2], Cécile Tremblay[7,8], Sharmistha Mishra[9,10,11], Mathieu Maheu-Giroux[1§]

[1]Department of Epidemiology and Biostatistics, School of Population and Global Health, McGill University, Montréal, QC

[2]Direction Régionale de Santé Publique de Montréal, Montréal, QC

[3]Clinical Outcomes Research and Evaluation, Research Institute - McGill University Health Centre, Montréal, QC

[4]Institut national de santé publique du Québec, Québec, QC

[5]Centre de recherche du CHU de Québec – Université Laval, Québec, QC

[6]Département de médecine sociale et préventive, Université Laval, Québec, QC

[7]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC

[8]Department of Microbiology Infectiology and Immunology, University of Montréal, Montréal, QC

[9]Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, ON

[10]Institute of Medical Sciences, University of Toronto, Toronto, ON

[11]Institute of Health Policy Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON

[§]**Corresponding Author:** Dr. Mathieu Maheu-Giroux

Address for Correspondence: mathieu.maheu-giroux@mcgill.ca

Key Words: HIV infections, Epidemics, Sexual and gender minorities, Drug use, Epidemiological models, Epidemiologic measurements

Word Count: 3,735

Abstract

Introduction: Men who have sex with men (MSM) and people who inject drugs (PWID) are disproportionately impacted by the HIV epidemic in Canada. Having the second-highest provincial diagnosis rate, an improved understanding of the epidemic among these populations in Québec could aid ongoing elimination efforts. We estimated HIV incidence and other epidemic indicators among MSM and PWID in Montréal and across Québec using a back-calculation model synthesizing surveillance data.

Methods: We developed a deterministic, compartmental mathematical model stratified by age, HIV-status, and disease progression and clinical care stages. Using AIDS and HIV diagnoses data, including self-reported time since last negative test and laboratory results of CD4 cell count at diagnosis, we estimated HIV incidence in each population over 1975-2020 by modeling a cubic M-spline. The prevalence, undiagnosed fraction, fraction diagnosed that started antiretroviral treatment (ART), and median time to diagnosis were also estimated. Since the COVID-19 pandemic disrupted testing, we excluded 2020 data and explored this in sensitivity analyses.

Results: HIV incidence in all populations peaked early in the epidemic. In 2020, an estimated 97 (95%CrI: 33-227) and 266 (95%CrI: 103-508) acquisitions occurred among MSM in Montréal and Québec, respectively. Among PWID, we estimated 2 (95%CrI: 0-14) and 6 (95%CrI: 1-26) acquisitions in those same regions. With 2020 data, unless testing rates reduced by 50%, these estimates decreased, except among Québec PWID, whose increased. Among all, the median time to diagnosis shortened to <2 years before 2020 and the undiagnosed fraction decreased to <10%. This fraction was higher in younger MSM, with 21.2% of 15-24 year-olds living with HIV in Montréal (95%CrI: 8.5-39.0%) and 31.1% in Québec (95%CrI: 17.0-47.5%) undiagnosed by 2020 year-end. Finally, ART access neared 100% in all diagnosed populations.

Conclusions: HIV incidence has drastically decreased in MSM and PWID across Québec, alongside significant improvements in diagnosis and treatment coverage –and the 2013 introduction of pre-exposure prophylaxis. Despite this, HIV transmission continued. Effective efforts to halt this transmission and rapidly diagnose people who acquired HIV,

especially among younger MSM, are needed to achieve elimination. Further, as impacts of the COVID-19 pandemic on HIV transmission are understood, increased efforts may be needed to overcome these.

Introduction

We have the biomedical tools to eliminate HIV [1]. Yet, transmission continues to occur in Canada. In fact, HIV diagnoses have recently stabilized at counts near those observed in the late 1990s [2, 3]. Across Canada, key populations, including men who have sex with men (MSM) and people who inject drugs (PWID), are disproportionately burdened by the HIV epidemic. In Québec, which had the second-highest provincial HIV diagnosis rate in 2019 [2], only 3.4% of adult men reported sex with another man in the previous 12 months [4]. Yet, MSM accounted for 71% of new male diagnoses that year [5]. People who ever injected drugs comprised 0.8% of Québec adults [4], but 0.7%-5.5% of new diagnoses in recent years belonged to that population [5].

In 2016, Canada endorsed the *Joint United Nations Programme on HIV/AIDS* (UNAIDS) efforts to end the HIV/AIDS epidemic as a public health threat [6]. Cities, where key populations often reside, play a crucial role in HIV epidemics [7]. Québec's epidemic epicentre lies in Montréal where 61% of new 2019 diagnoses occurred [5]. In 2017, Montréal became the first UNAIDS Fast-Track City in Canada, committing to HIV elimination by 2030 [8, 9]. Interim, 2020 targets aimed for zero new acquisitions, a strengthened treatment and care cascade (reaching 95% diagnosis coverage, 95% of those diagnosed on treatment, and, of those, 95% virally suppressed by 2025), zero discrimination, and zero stigma [10]. Measuring the target of zero new acquisitions is difficult as it cannot be directly observed. New diagnoses have been used as a proxy [10]; however, these reflect mostly past incidence and are affected by testing efforts. Analyses discerning new acquisitions from diagnoses while accounting for testing trends are needed.

Timely estimates of new acquisitions are necessary to monitor progress towards elimination and identify unmet prevention needs. Doing so requires modeling tools synthesizing surveillance data, allowing the back-calculation of HIV incidence using information such as CD4 cell count at diagnosis and HIV testing history [11]. The *Public Health Agency of Canada* (PHAC) estimates HIV incidence using a statistical back-calculation method based on HIV and AIDS diagnoses and HIV/AIDS-related deaths [12]. Overall national and provincial estimates, and those stratified by exposure category (e.g., MSM, PWID), are typically produced and provided to provincial public health authorities.

Overall Québec estimates have been reported up to 2018 [13]. However, the last publicly reported exposure category estimates for Québec are from 2011 [14]. Moreover, age-stratified and city-level estimates are not available.

To inform provincial elimination efforts, we aimed to estimate HIV incidence in Québec and its largest city (Montréal) over 1975-2020, stratified by age, for two key populations: MSM and PWID. We simultaneously estimated key HIV epidemic metrics of prevalence, undiagnosed fraction, and time to diagnosis. We achieved this by developing, parameterizing, and calibrating a multi-state back-calculation mathematical model synthesizing granular surveillance data and capturing the disease's natural progression and treatment and care cascade. These metrics can provide detailed information for communities and health authorities to identify unmet prevention needs and sustainably curb HIV transmission.

Methods

Data sources

We obtained surveillance data on AIDS cases (1979-1998) and new HIV diagnoses (2003-2020) from the *Institut national de santé publique du Québec* (INSPQ). The AIDS data are aggregated and stratified by exposure category and sex. The HIV diagnosis data are annual and stratified by region, exposure category, sex, age, self-reported time since last negative test, and CD4 cell count at diagnosis. The exposure categories are mutually exclusive and assigned hierarchically, with men who had sex with another man classified as MSM and those who injected drugs as PWID. Those who both had sex with another man and injected drugs are categorized separately and not considered here.

Modeling framework

We developed a deterministic, compartmental mathematical model using Bayesian back-calculation methods to estimate HIV incidence over 1975-2020 among distinct, open populations of MSM and PWID (active and past injectors) aged 15-99 years. Extending the approaches of others [15, 16], we stratified the population of interest (MSM, PWID) by HIV status and, among people living with HIV (PLHIV), by primary infection and CD4

cell count categories, diagnosed status, and treatment status (untreated, ever treated) (Figure 6.2.1). The model is further stratified by 5-year age groups.

Individuals enter the model susceptible to HIV acquisition (Figure 6.2.1). Those that acquire HIV progress to the primary stage, where the model assumes no diagnoses occur. After this short period, individuals enter the different CD4 cell count compartments, some at lower counts [17, 18]. The subsequent horizontal flow models disease progression through decreasing CD4 cell count. The vertical flow models the clinical care cascade of diagnosis and starting antiretroviral therapy (ART). Individuals exit the model due to all-cause, injection-related (active PWID), or AIDS-related mortality.

The model is solved using a Euler algorithm and 0.01-year time step, coded in R (v.4.0.3) using a C++ back-end via the Rcpp library [19-21]. Analyses are conducted separately by exposure category, sex, and region (Montréal and the whole province), with Montréal defined by the public health unit "*région sociosanitaire 06*".

HIV incidence estimation

We modeled HIV transmission over 1975-2020 using a smooth incidence curve formed with cubic M-splines [16, 22], setting the first coefficient to zero. The incidence rate denominator comprises those at risk of acquiring HIV: all susceptible MSM and actively injecting PWID, respectively. Where feasible, we modeled age-stratified incidence by estimating a random effect per 10-year age group. Finally, we varied the number and location of spline knots and determined the best fitting incidence curve considering both the Watanabe–Akaike information criterion (WAIC) and leave-one-out cross-validation information criterion (LOOIC).

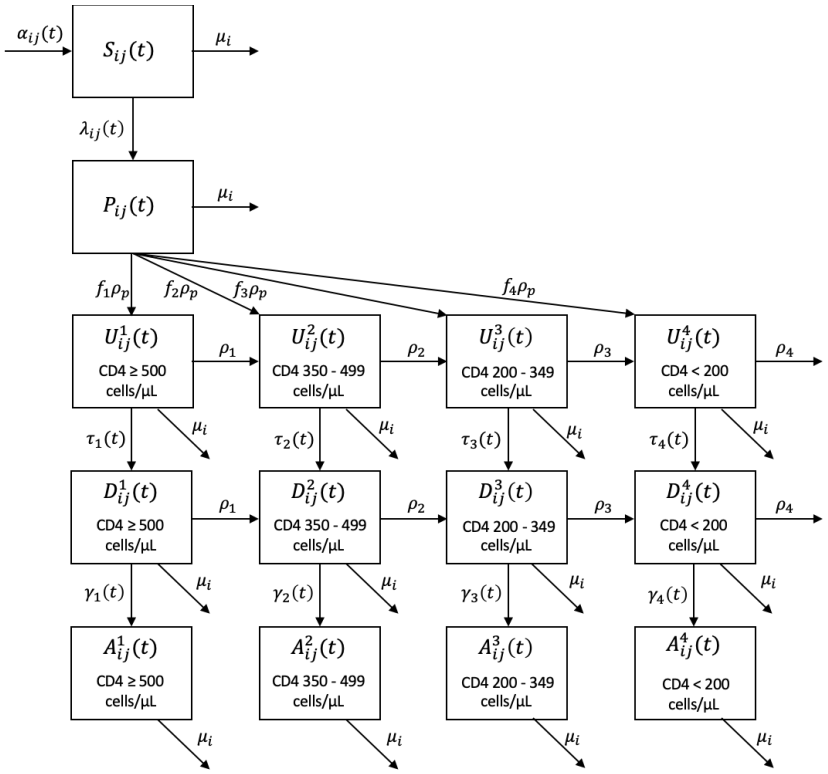

Figure 6.2.1. Model Flow Diagram

The index *i* indicates age group (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+), *j* indicates sex (male, female, overall), and *k* indicates disease stage (1=CD4 ≥500 cells/μL; 2=CD4 350-499 cells/μL; 3=CD4 200-349 cells/μL; and 4=CD4 <200 cells/μL). At time *t*, $S_{ij}(t)$ is the number of susceptible individuals, $P_{ij}(t)$ is the number of individuals with primary infection, $U_{ij}^k(t)$ is the number of individuals undiagnosed in each of the CD4 cell count compartments, $D_{ij}^k(t)$ is the number of individuals diagnosed and untreated in each of the CD4 cell count compartments, and $A_{ij}^k(t)$ is the number of individuals diagnosed who initiated ART in each of the CD4 cell count compartments. See Table 6.3.9 of the supplementary materials for a full description of model parameters.

Parameterization: demography, testing, and ART initiation

Demographic information was drawn from census data, population-based health surveys, and vital statistics (supplementary materials). The MSM and PWID (ever injected) population sizes were assumed proportional to the male and total populations, respectively. The active PWID population decreased with time (Figure 6.3.1), informed by local

estimates [23-25]. Disease progression was parameterized by scientific literature. Where possible, local studies informed the testing and ART parameters. Table 6.3.9 details all parameter sources.

We modeled HIV testing and diagnosis among those susceptible to and living with HIV. Testing rates differed by CD4 cell count, reflecting asymptomatic and symptomatic testing. Except for symptomatic diagnoses among those with CD4 <200 cells/μL, testing started in 1985 and subsequently increased over time. It was modeled using a flexible logistic growth function capturing testing trends that reflect treatment advances, testing recommendations, and recent empirical estimates. Upon a first positive test, a certain proportion of HIV diagnoses are reported to the surveillance database. Others, at times, may be delayed and classified as such ("delayed report"). The model accounts for these using a reporting fraction varying between 2003-2011 and 2012-2020, as the surveillance system started including those without Québec's universal health insurance in 2012.

ART initiation rates varied by time and CD4 cell count to match guideline changes. These indicated ART for those with CD4 ≤350 cells/μL from 1996-2012 [26-28], ≤500 cells/μL from 2013-2015 [27-29], and all PLHIV from 2016 onward [29]. Accordingly, all ART initiation rates were zero until 1996 (upon highly active ART availability) or until the eligibility criteria indicated use. The rate additionally varied between 1996-2003 and 2004-2012, with a higher rate in the latter reflecting increasing access and acceptability over time. The rates were fixed and assumed equal across eligible categories.

Model calibration

We calibrated the model to the following outcomes, excluding 2020 data due to uncertainties in how testing disruptions during the COVID-19 pandemic impacted the observed diagnoses: 1) aggregated AIDS cases (1979-1998); 2) annual HIV diagnoses by sex and age (2003-2019), and CD4 cell count at diagnosis (2013-2019); and 3) annual proportion of diagnoses reporting a negative HIV test result <12 months ago by sex and age (2003-2019). In estimating the age-specific incidence, we grouped the data by 10-year age categories to avoid small counts of diagnoses and ensure stability of estimates. CD4 cell count had missing data (12% and 11% among MSM and 22% and 19% among PWID

in Montréal and Québec, respectively), which were assumed to be missing completely at random. Regarding testing history, individuals that were unsure when last tested (<4% of observations) were considered not to have been tested for HIV in the past 12 months. As reported elsewhere [30], initial cross-validation suggested that self-reports of a negative test <12 months ago were subject to a telescoping bias. We accounted for this by assuming these self-reports referred to periods up to 18 months.

We adopted a Bayesian calibration framework. Specifically, we used maximum a posteriori estimation [31] with prior distributions elicited for each unknown parameter (Table 6.3.9). Point estimates were obtained by minimizing the negative posterior log-likelihood of the model. This optimization occurred in two steps. First, we defined a distribution using a Broyden-Fletcher-Goldfarb-Shanno algorithm with starting values from the Nelder-Mead algorithm [32]. Secondly, to approximate the posterior distribution, we performed sampling importance resampling using 50,000 parameter sets from that proposal (i.e., multivariate *t*-distribution) and resampling 1,000 sets without replacement, applying standardized importance weights. We summarized posterior distributions using the median. The 2.5^{th} and 97.5^{th} percentiles approximated 95% credible intervals (CrI).

Additional epidemic metrics

With the estimated incidence curve, we calculated the HIV prevalence (total PLHIV/total population), the fraction undiagnosed (total in primary and undiagnosed compartments/total PLHIV), and the fraction of diagnosed PLHIV that started ART (total in ever treated compartments/total in diagnosed (untreated) and ever treated compartments). Lastly, we calculated the median time to diagnosis annually using period life tables [33]. Each life table began with the total new acquisitions from a given year and, over time, counted diagnoses from each CD4 cell count category or upon AIDS-related death, assuming those that acquired HIV were subject to that same year's testing rate throughout their lifetime.

Sensitivity Analyses

Due to uncertainties in the active PWID population size, we varied the assumed size to assess the impact on mortality. We also varied some of the assumed parameters for disease

progression and treatment initiation, as described in the supplement (Appendix 5). Lastly, calibrating up to 2019 data and predicting incidence through 2020 assumes incidence was unaffected by the COVID-19 pandemic. In sensitivity analyses, we included 2020 data in calibration and assessed the incidence with 0%, 25%, and 50% reductions in testing rates over March-December 2020.

Ethics

This study received ethics approval from the *McGill University Research Ethics Board* (REB#: *A12-E84-18A*). Consent was not necessary as we used aggregated information (from de-identified and anonymized databases) from routinely collected surveillance data.

Results

Surveillance data

From 1979-1998, 3,582 AIDS cases classified as MSM were reported across Québec [34], with 2,791 from Montréal [35]. Over that same period, 375 AIDS cases classified as PWID were reported provincially [34], with 300 from Montréal [35]. The new HIV diagnoses reported over 2003-2019 among MSM totalled 3,488 and 2,286 across Québec and Montréal, respectively. Of these, 23% and 26% reported recently testing negative in those same regions. Among PWID, 390 and 174 new HIV diagnoses were reported in Québec and Montréal, respectively, 10% of which recently tested negative in both regions. Lastly, since 2013, the CD4≥500 cells/μL category had the highest proportion of reported new diagnoses, comprising 40% and 43% of MSM diagnoses and 31% and 38% of PWID diagnoses in Québec and Montréal, respectively.

Model selection and fits

Our calibrated models reproduced the surveillance data and key epidemic features (Figure 6.2.2 and Figure 6.3.4-Figure 6.3.9), with almost all data points falling within the modeled uncertainty bounds. The best-fitting models had 3-5 knots depending on strata (Table 6.3.13). In general, the WAIC did not change substantially across the models explored.

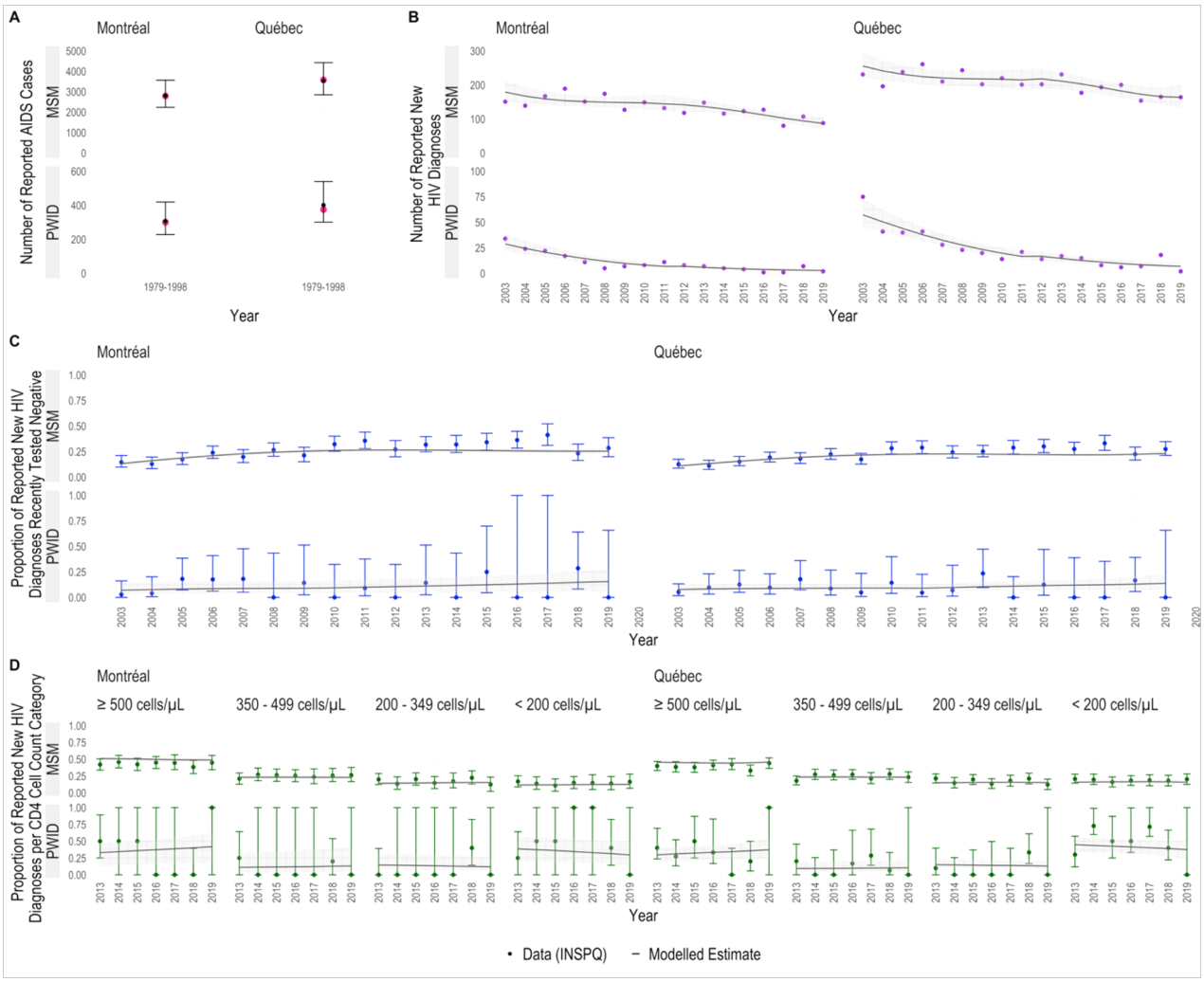

Figure 6.2.2. Model fits

Model fits to the calibration outcomes among men who have sex with men (MSM) and people who inject drugs (PWID) in Montréal and the province of Québec: A) number of reported AIDS cases; B) number of reported new HIV diagnoses; C) proportion of reported new HIV diagnoses that recently tested negative (<18 months ago); and D) proportion of reported new HIV diagnoses per CD4 cell count category. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The colored points and bars display the outcomes from the *Institut national de santé publique du Québec* (INSPQ) data and their corresponding 95% confidence intervals, where applicable.

Epidemic trajectory: men who have sex with men

The HIV incidence curves among MSM exhibited two peaks throughout the epidemic. The first, in the mid-1980s, reached highest and impacted all ages. Montréal MSM had the highest overall incidence rate of 1.2 per 100 person-years (PY; 95%CrI: 0.9-1.6 per 100 PY) at its first peak in 1985, with 501 (95%CrI: 397-640) acquisitions that year (Figure 6.2.3). The provincial MSM epidemic closely followed this trend, albeit with a smaller peak of 0.8 per 100 PY (95%CrI: 0.6-1.0 per 100 PY), but 617 (95%CrI: 493-778) acquisitions. For more than a decade afterward, incidence among MSM declined. Nevertheless, it again started trending upward by the end of the 1990s. Around then, differences in the estimated age-stratified incidence became apparent, increasing considerably in those aged 25-34 and 35-44 years (Figure 6.2.4, Figure 6.3.10). After reaching an overall rate of 0.4 per 100 PY (95%CrI: 0.3-0.6 per 100 PY) and 0.3 per 100 PY (95%CrI: 0.2-0.4 per 100 PY) in the mid-to-late-2000s in Montréal and Québec, respectively, this trend reversed. Finally, in 2020, incidence potentially increased. At 2020 year-end, the estimated incidence rate was 0.2 per 100 PY (95%CrI: 0.0-0.5 per 100 PY) and 0.3 (95%CrI: 0.1-0.6 per 100 PY) in Montréal and Québec, with 97 (95%CrI: 33-227) and 266 (95%CrI: 103-508) acquisitions estimated that year in each region, respectively (Table 6.2.1, Figure 6.2.3).

HIV prevalence followed a trend similar to incidence, peaking in the early 1990s at 9.5% (95%CrI: 7.6-12.0%) in Montréal and 6.3% (95%CrI: 5.1-7.8%) in Québec (Figure 6.2.5). After dipping slightly, following the peak in AIDS deaths (Figure 6.3.18), the prevalence continued rising until the mid-to-late-2010s. These trends were largely mimicked across age groups, except for those <35 years, whose prevalence stabilized (Figure 6.3.11). By 2020 year-end, prevalence in MSM was estimated at 10.4% (95%CrI: 8.3-12.6%) in Montréal and 7.8% (95%CrI: 6.2-9.2%) provincially (Figure 6.2.5).

The undiagnosed fraction decreased upon testing availability in 1985 (Figure 6.2.5). Among MSM, an estimated 4.3% (95%CrI: 2.3-7.2%) and 7.9% (95%CrI: 4.6-12.4%) of PLHIV in Montréal and Québec, respectively, were undiagnosed at 2020 year-end (Table 6.2.1, Figure 6.2.5). Correspondingly, up to the start of 2020, the median time to diagnosis decreased to 1.5 (95%CrI: 1.3-1.7 years) and 1.9 years (95%CrI: 1.7-2.1 years) in those

same regions (Figure 6.2.5). Important differences in the percentage undiagnosed were observed in younger MSM, especially 15-24 year-olds, among whom 21.2% in Montréal (95%CrI: 8.5-39.0%) and 31.1% in Québec (95%CrI: 17.0-47.5%) remained undiagnosed by the end of 2020 (Figure 6.3.12). Lastly, the percentage of diagnosed PLHIV that started ART increased over time, reaching almost 100% (Figure 6.2.5, Figure 6.3.13).

Sensitivity analyses incorporating testing reductions and including 2020 data in calibration resulted in lower incidence unless testing was reduced by 50%, where it was similar to our main results (Figure 6.3.19-Figure 6.3.21, Table 6.3.14). The undiagnosed fraction was also lower, unless testing was reduced by 25% and 50%, where it was similar to and possibly higher than our main estimates.

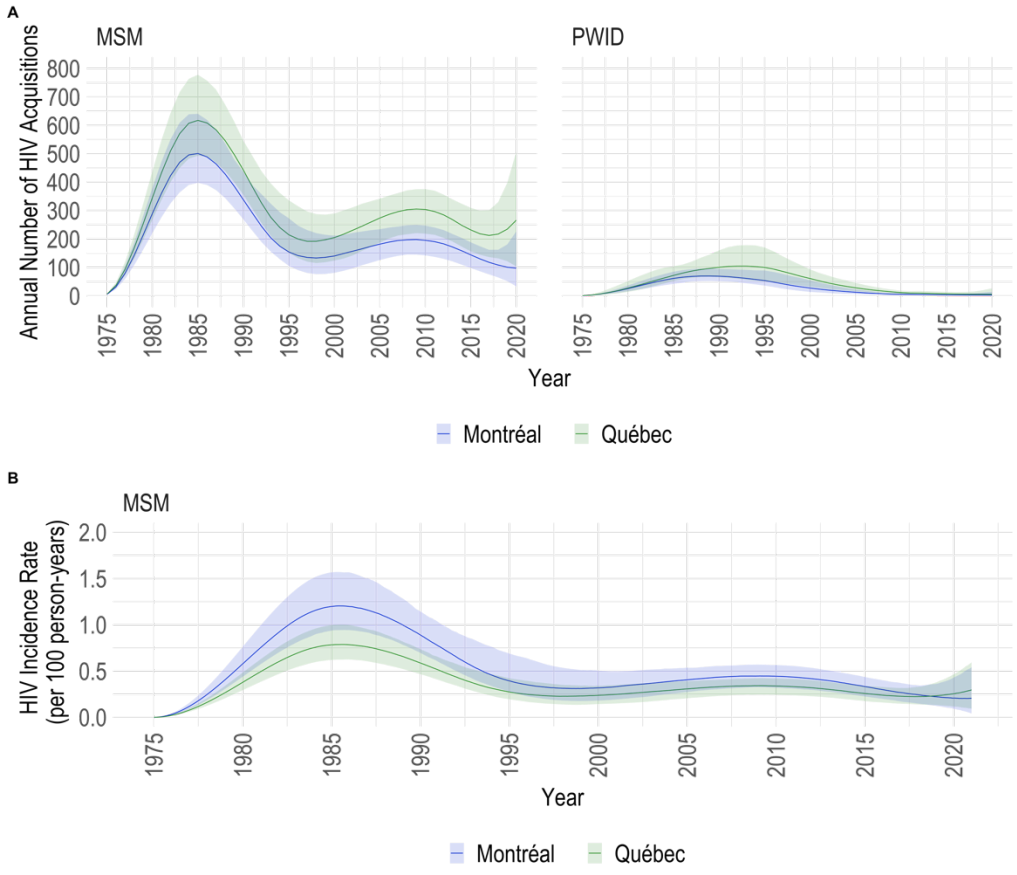

Figure 6.2.3. Overall HIV Incidence
Estimated HIV incidence over 1975-2020 among men who have sex with men (MSM) and people who injected drugs (PWID) in Montréal and the province of Québec: A) the annual number of HIV acquisitions among MSM and active PWID; and B) the HIV incidence rate

among MSM. Incidence rates are not presented for PWID due to uncertainties in the denominator (the active PWID population size over time). The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for the province of Québec.

Table 6.2.1. Estimates of HIV incidence and fraction undiagnosed, 2017-2020
Estimated HIV incidence rate, annual number of HIV acquisitions, and percentage of people living with HIV undiagnosed in recent years (2017-2020) among men who have sex with men and people who inject drugs in Montréal and the province of Québec.

Location	Year	Incidence rate (95%CrI) per 100 PY at year end†	Annual number of HIV acquisitions (95%CrI)	% PLHIV undiagnosed (95%CrI) at year end
Men who have sex with men				
Montréal	2017	0.2 (0.2-0.3)	118 (75-162)	5.3 (3.5-7.3)
	2018	0.2 (0.1-0.4)	108 (65-162)	4.8 (3.1-6.9)
	2019	0.2 (0.1-0.4)	100 (51-181)	4.5 (2.8-6.9)
	2020	0.2 (0.0-0.5)	97 (33-227)	4.3 (2.3-7.2)
Province of Québec	2017	0.2 (0.1-0.3)	212 (136-301)	8.0 (5.7-11.0)
	2018	0.2 (0.1-0.4)	217 (132-330)	7.7 (5.3-10.9)
	2019	0.3 (0.1-0.5)	234 (122-397)	7.6 (5.0-11.2)
	2020	0.3 (0.1-0.6)	266 (103-508)	7.9 (4.6-12.4)
People who inject drugs (includes active and past injectors)				
Montréal	2017	-	3 (1-8)	2.1 (0.7-6.2)
	2018	-	3 (1-9)	1.9 (0.6-6.0)
	2019	-	2 (0-11)	1.8 (0.5-6.0)
	2020	-	2 (0-14)	1.6 (0.4-7.1)
Province of Québec	2017	-	6 (3-14)	3.4 (1.6-7.4)
	2018	-	6 (2-15)	3.1 (1.4-7.2)
	2019	-	6 (2-20)	2.9 (1.2-7.2)
	2020	-	6 (1-26)	2.8 (1.0-8.0)

Abbreviations: Credible interval (CrI); person-years (PY); people living with HIV (PLHIV).

†Only presented for men who have sex with men, due to uncertainties in the denominator for people who inject drugs (active injectors).

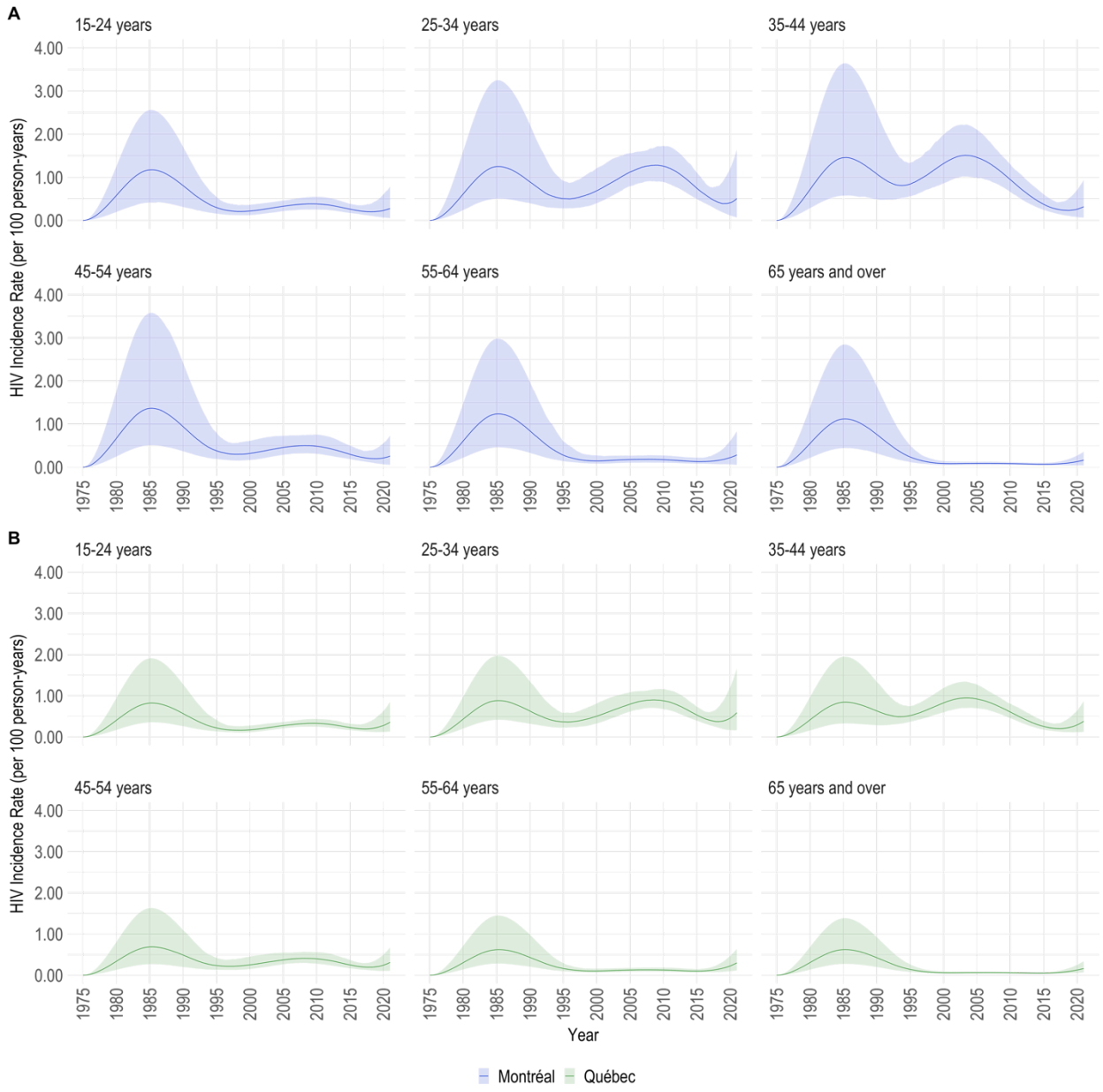

Figure 6.2.4. Age-stratified HIV incidence

Estimated age-stratified HIV incidence rate over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec, aggregated by 10-year age groups. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region (panel A) and green representing estimates for the whole province (panel B).

Epidemic trajectory: people who inject drugs

The HIV incidence curve among actively injecting PWID had one peak. The highest annual incidence occurred in the late-1980s-to-early-1990s with 70 (95%CrI: 53-96) and 105 (95%CrI: 56-179) acquisitions in Montréal and the province, respectively. After these peaks, incidence trended downward (Figure 6.2.3). In 2020, 2 (95%CrI: 0-14) and 6 (95%CrI: 1-26) acquisitions were estimated in Montréal and Québec, respectively (Table 6.2.1, Figure 6.2.3). Similar regional trends were seen among active male and female PWID (Figure 6.3.14), but with wider uncertainty ranges and more acquisitions estimated among males. Due to uncertainties in the active PWID population size, incidence rates are not presented for this population.

HIV prevalence among lifetime PWID increased until the late-1990s-early-2000s, reaching 3.3% (95%CrI: 2.5-4.7%) and 2.4% (95%CrI: 1.6-3.7%) in Montréal and Québec, respectively (Figure 6.2.5). As AIDS-related deaths diminished (Figure 6.3.18) and incidence somewhat levelled off, prevalence stabilized and decreased slowly to 2.4% (95%CrI: 1.7-3.5%) in Montréal and 1.8% (95%CrI: 1.2-2.6%) in Québec by 2020 year-end. When stratified by sex, similar trends were estimated (Figure 6.3.15).

The PWID population also saw large declines in the undiagnosed fraction (Figure 6.2.5, Figure 6.3.15). By 2020 year-end, 1.6% (95%CrI: 0.4-7.1%) and 2.8% (95%CrI: 1.0-8.0%) of PLHIV were undiagnosed in Montréal and Québec, respectively (Table 6.2.1, Figure 6.2.5). The median time to diagnosis also decreased up to 2020, reaching 1.3 (95%CrI: 0.8-3.4) and 1.8 (95%CrI: 1.0-3.2) years in those regions (Figure 6.2.5). Finally, the percentage of diagnosed PLHIV that started ART similarly increased to almost 100% (Figure 6.2.5, Figure 6.3.15).

None of these results were appreciably impacted by the active PWID population size or ART initiation rates. Including 2020 data in calibration did affect results (Figure 6.3.19-Figure 6.3.21, Table 6.3.14). Among Montréal PWID, there were potentially fewer acquisitions in 2020, even with testing reduced by 50%. In contrast, acquisitions and the undiagnosed fraction increased among PWID across Québec as, in this case, the observed diagnoses substantially increased from 2019 to 2020.

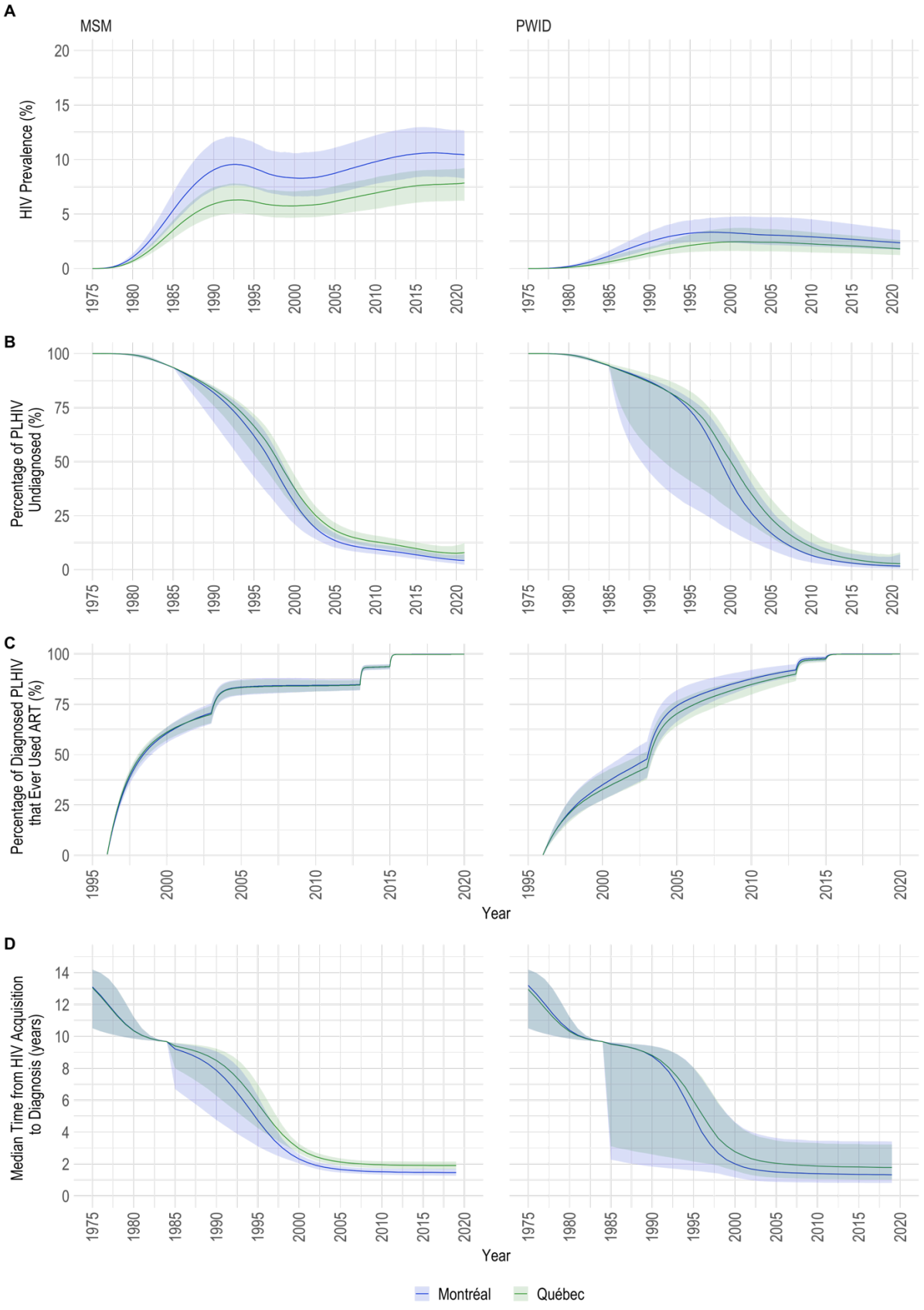
A
MSM
PWID
HIV Prevalence (%)
B
Percentage of PLHIV Undiagnosed (%)
C
Percentage of Diagnosed PLHIV that Ever Used ART (%)
Year
D
Median Time from HIV Acquisition to Diagnosis (years)
Year
Montréal
Québec

Figure 6.2.5. Additional epidemic metrics
Estimated HIV prevalence (panel A), percentage of people living with HIV (PLHIV) undiagnosed (panel B), percentage of diagnosed PLHIV that ever used antiretroviral treatment (ART; panel C), and median time from HIV acquisition to diagnosis (panel D) over 1975-2020* among men who have sex with men (MSM) and people who ever injected drugs (PWID) in Montréal and the province of Québec. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for the whole province. *Estimates of the median time from HIV acquisition to diagnosis are presented up 2019 year-end due to uncertainties in testing rates at the start of the COVID-19 pandemic in 2020.

Discussion

Accurately measuring progress towards elimination is challenging, yet, synthesizing complex information from surveillance and other data can help overcome some limitations. We developed a multi-state back-calculation Bayesian model and estimated key elimination indicators of new HIV acquisitions, the burden of disease, and the cascade of care. Our findings suggest that –among key populations historically bearing the highest burden– HIV incidence has drastically decreased and, in MSM, may have reached near to 0.1 per 100 PY, the proposed elimination threshold for HIV as a public health threat. However, the goal of zero new acquisitions was not achieved and could be further from sight due to HIV services interruptions during the COVID-19 pandemic. While less than 14 acquisitions could have occurred among PWID in Montréal, we projected 97 (95%CrI: 33-227) acquisitions in 2020 among MSM. Across the province, 6 (95%CrI: 1-26) acquisitions in PWID and 266 (95%CrI: 103-508) in MSM were projected.

Our results also point to rapid and robust improvements in the treatment and care cascade. The fraction of undiagnosed PLHIV is estimated at 4.3% (95%CrI: 2.3-7.2%) among Montréal's MSM, a finding supported by the *Engage* cohort [36, 37], and 1.6% (95%CrI: 0.4-7.1%) among PWID. Therefore, Montréal has already reached the 2025 goal of 95% diagnosed among these populations. However, setbacks could have occurred since the COVID-19 pandemic began. Provincially, slightly higher proportions were unaware of

their status: 7.9% of MSM (95%CrI: 4.6-12.4%) and 2.8% of PWID (95%CrI: 1.0-8.0%). Previous studies suggested PLHIV residing outside of urban areas could face additional barriers in accessing healthcare, including stigma, further distance to providers coupled with inadequate transportation, and local providers being less experienced with HIV and/or key populations [38, 39]. There were also proportionally more young MSM unaware of their status, highlighting their unmet prevention needs. Lower diagnosis coverage among younger PLHIV also reflects HIV's transmission dynamics: young people have higher incidence and smaller cumulative testing exposure [33, 40]. Concomitant with diagnosis coverage improvements, we estimated shortened diagnostic delays. Still, further reductions could impact onward transmission if linkage to care is prompt.

Finally, almost 100% of diagnosed PLHIV have taken ART -in line with empirical estimates from a Montréal clinical cohort [41] and *Engage* [36], suggesting high proportions of diagnosed PLHIV are being linked to care. While this does not speak to current use or levels of viral suppression, these studies did estimate >95% of those diagnosed were on ART and, of those, >88% were virally suppressed [36, 41]. Although we do not model the impact of ART on transmission directly, its successful scale-up likely played a part in the incidence declines over the last decade. Moreover, pre-exposure prophylaxis (PrEP) was introduced for MSM in 2013 and could have accelerated incidence reductions, especially amidst increased usage in recent years [42, 43], where coverage (i.e., those currently on PrEP) rose from 5% to 10% between 2017 and 2018 in Montréal [43].

Given the richness and granularity of Québec's HIV surveillance data, we tailored our model to its intricacies. PHAC's back-calculation method is general to accommodate the different provincial data streams. We explicitly describe the clinical course of HIV, allow testing rates per disease stage, and calibrate to multiple sources of recency information, all of which could more accurately estimate incidence. Moreover, modeling ART captures reduced mortality and improves our prevalence estimation. The trends in incidence did follow those modeled by PHAC until 2011 among MSM and PWID in Canada [14]. Their 2011 Québec-specific estimates suggested 425 (290-560) and 9,690 (7,880-11,500) MSM acquired and were living with HIV that year, respectively [14]. Among PWID, they estimated that there were 60 (40-80) acquisitions and 3,000 (2,400-3,600) PLHIV [14]. In

that same year, we projected fewer acquisitions (297, 95%CrI: 215-370 in MSM and 10, 95%CrI: 6-17 in PWID) and a smaller population of PLHIV (6,928, 95%CrI: 5,469-8,334 MSM and 1046, 95%CrI: 689-1,544 PWID). Despite possibly underestimating incidence in the mid-1990s, from 2000 onward our MSM incidence rate and prevalence estimates reassuringly aligned with that observed by cohort studies in Montréal (Figure 6.3.16Figure 6.3.17).

This study has several limitations. First, the paucity of data informing the active PWID population sizes, and potential underrepresentation of active PWID in the available estimates, necessitated additional assumptions in this regard. Therefore, we did not provide HIV incidence rates for PWID and focused on acquisitions. Moreover, we lacked appropriate PWID cross-validation data as local studies [44, 45] have focused solely on individuals actively injecting whereas we modeled all people who ever injected drugs. Further, despite modeling reporting delays, we did not have strong estimates to inform them. However, we believe most transmissions occurring and diagnosed in Québec have a high probability of being reported without delay, and our calibrated reporting fractions reflect this (approximately 70-80% across populations). Concerning demography, we do not capture migration of PLHIV. Not unlike other models, this could affect the prevalence and undiagnosed fraction, the extent to which depends on the level and direction of the net migration of PLHIV in the MSM and PWID populations. In our setting, we expect net migration to be small and our estimates to be robust. Our cross-validation to the Engage study's prevalence is also reassuring. Finally, HIV testing could have fluctuated in recent years. Potential increases alongside PrEP scale-up, for example, could identify more undiagnosed PLHIV through consultations, leading our model to overestimate incidence [46]. Despite this, the number of diagnoses remained relatively stable. On the other hand, the COVID-19 pandemic disrupted testing in 2020 and the extent to which is not yet known [47]. Thus, we explored this in sensitivity analyses.

Conclusions

The UNAIDS Fast-Track City goals are ambitious. Meeting and maintaining targets of zero new HIV acquisitions, 95% diagnosis coverage, 95% treatment coverage, and 95% viral suppression requires an actionable response and epidemic monitoring. Leveraging detailed

surveillance data complemented by other sources, we provided up-to-date estimates of important epidemic metrics among key populations in Montréal and across Québec. This work demonstrates how such back-calculation mathematical models can be applied in a Canadian context to estimate incidence, compared to only monitoring diagnoses, and other jurisdictions with similar data could do the same. Identifying effective policies to progress towards and sustain elimination is crucial, especially in light of the possible setbacks from the decline in prevention service access and use during the COVID-19 pandemic [47]. Future work exploring the population-level impact of interventions that could be scaled-up, such as PrEP, could inform these.

Competing interests: JC has investigator-sponsored research grants from Gilead Sciences Canada and ViiV Healthcare. He has also received financial support for conference travel and advisory work for Gilead Sciences Canada, Merck Canada and ViiV Healthcare. MM-G reports an investigator-sponsored research grant from *Gilead Sciences Inc*., outside of the submitted work, and contractual arrangements from the *World Health Organization*, the *Joint United Nations Programme on HIV/AIDS* (UNAIDS), the *Institut national de santé publique du Québec* (INSPQ), and the *Institut d'excellence en santé et services sociaux* (INESSS) also outside of the submitted work. CT has investigator-sponsored research grants from Merck and Gilead, and has received financial support for advisory work and conferences from Gilead, Merck, Medicago, Astra-Zeneca, and GSK. MA is recipient of a Foundation grant from the Canadian Institutes of Health Research outside the submitted work and reports contractual arrangements with the Public Health Agency of Canada and the Ministère de la santé et des services sociaux du Québec supporting the study that provided the data on people who inject drugs used in the present study.

Authors' contributions: CMD, MMG, and JC contributed to the study conception and design. RB, MA, and GL were involved in the design and data collection. Analyses were performed by CMD, with support from MMG. The manuscript was drafted by CMD. All authors contributed to the interpretation of results and reviewed the manuscript for important intellectual content. Overall supervision for this project was provided by MMG and JC. All authors approved the final manuscript.

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6.3. Manuscript 3: Supplementary Materials

6.3.1. Appendix 1

Model equations

Let *i* indicate age group (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+), *j* indicate sex (male, female, overall), *t* indicate time in years, and *k* indicate CD4 cell count compartment (CD4≥500 cells/μL, CD4 350-499 cells/μL, CD4 200-349 cells/μL, and CD4<200 cells/μL). The following system of ordinary differential equations (with parameters as defined in Table 6.3.9) describes the occurrence of events over time *t* in the model.

1. HIV-susceptible (S) individuals are modeled according to:

$$\frac{dS_{ij}(t)}{dt} = \alpha_{ij}(t) - \lambda_{ij}(t)\delta_j(t)S_{ij}(t) - \mu_i(t)S_{ij}(t) \quad (1)$$

where $\delta_j(t)$ is a weight to obtain the number of susceptible individuals that are at-risk of HIV acquisition.

2. The number of people in the primary infection phase (P) are modeled according to:

$$\frac{dP_{ij}(t)}{dt} = \lambda_{ij}(t)\delta_j(t)S_{ij}(t) - \big(\rho_p + \mu_i(t)\big)P_{ij}(t) \quad (2)$$

3. The number of undiagnosed individuals (U) in the different $CD4^+$ cell count compartments *k* are modeled according to:

$$\frac{dU_{ij}^k(t)}{dt} = \rho_p f_k P_{ij}(t) - (\tau_k(t) + \rho_k + \mu_i(t))U_{ij}^k(t); \quad if\ k = 1 \quad (3.1)$$

$$\frac{dU_{ij}^k(t)}{dt} = \rho_p f_k P_{ij}(t) + \rho_{(k-1)}U_{ij}^{k-1}(t) - (\tau_k(t) + \rho_k + \mu_i(t))U_{ij}^k(t); \quad if\ k = 2,3,4 \quad (3.2)$$

4. The number of diagnosed individuals that are not on treatment (D) are modeled according to:

$$\frac{dD_{ij}^{k}(t)}{dt} = \tau_k(t)U_{ij}^{k}(t) - (\gamma_k(t) + \rho_k + \mu_i(t))D_{ij}^{k}(t); \quad if\ k = 1 \qquad (4.1)$$

$$\frac{dD_{ij}^{k}(t)}{dt} = \tau_k(t)U_{ij}^{k}(t) + \rho_{(k-1)}D_{ij}^{k-1}(t) - (\gamma_k(t) + \rho_k + \mu_i(t))D_{ij}^{k}(t); \quad if\ k = 2,3,4 \ (4.2)$$

5. The number of diagnosed individuals on treatment (A) are modeled according to:

$$\frac{dA_{ij}^{k}(t)}{dt} = \gamma_k(t)D_{ij}^{k}(t) - \mu_i(t)A_{ij}^{k}(t) \qquad (5)$$

6.3.2. Appendix 2

Model demography

Population size and growth

Québec

We used provincial population estimates from Statistics Canada[3] to model the population size of Québec. As the province experience periods of growth over 1975–2021, we set the initial model population to the 1975 population size by sex and age group (Table 6.3.1) and applied a time-varying growth factor calculated from the overall and sex-stratified population data over 5-year periods assuming an exponential distribution (Table 6.3.2).

Montréal

To model the population size of Montréal, we used Canadian census data (1976–1991)[4-7] and Institut de la statistique du Québec (ISQ) population size estimates (1996–2021)[8] of the Montréal administrative region (i.e. the island of Montréal). From 1975-1986, this region experienced a population decline, after which the population again began to increase. As there remains uncertainty in the demographics of those who migrated out of Montréal during that time, like another mathematical model of HIV transmission among Montréal MSM developed by Milwid et al.[9], we assumed the Montréal population size was constant over 1975–1986. We used the population size of males and females per age group in 1986 to set Montréal's initial population in the model (Table 6.3.3). Subsequent growth of the Montréal population over 1986–2021 was modeled using a time-varying growth

factor calculated from the overall and sex-stratified population data over 5-year periods, assuming an exponential distribution (Table 6.3.4).

Table 6.3.1. Population size of Québec in 1975 by sex and age[3]

Age group (years)	Population size		
	Male	Female	Total
15 – 19	342,560	332,085	674,645
20 – 24	315,832	310,638	626,470
25 – 29	286,538	280,007	566,545
30 – 34	238,742	231,951	470,693
35 – 39	188,075	183,920	371,995
40 – 44	181,940	180,788	362,728
45 – 49	174,267	178,320	352,587
50 – 54	158,232	167,433	325,665
55 – 59	127,130	137,522	264,652
60 – 64	111,039	123,272	234,311
≥65	199,612	263,468	463,080
Total (15 and over)	2,326,861	2,394,636	4,721,497

Table 6.3.2. Population size and exponential growth factor of Québec over 1975–2020 by sex[3]

	Population size			Growth factor			
Year	**Male**	**Female**	**Total**	**Years**	**Male**	**Female**	**Total**
1975	3,150,965	3,179,338	6,330,303	1975	-	-	-
1976	3,182,546	3,214,215	6,396,761	1976 – 1980	0.003	0.006	0.005
1981	3,237,077	3,310,130	6,547,207	1981 – 1985	0.004	0.005	0.005
1986	3,308,452	3,399,718	6,708,170	1986 – 1990	0.010	0.011	0.010
1991	3,481,065	3,586,331	7,067,396	1991 – 1995	0.005	0.005	0.005
1996	3,568,418	3,678,479	7,246,897	1996 – 2000	0.004	0.004	0.004
2001	3,647,738	3,748,718	7,396,456	2001 – 2005	0.007	0.006	0.006
2006	3,777,953	3,854,013	7,631,966	2006 – 2010	0.010	0.009	0.010
2011	3,971,988	4,033,102	8,005,090	2011 – 2015	0.006	0.005	0.005
2016	4,095,582	4,130,368	8,225,950	2016 – 2020	0.010	0.008	0.009
2021	4,304,047	4,300,448	8,604,495	-	-	-	-

Table 6.3.3. Population size of the administrative region of Montréal in 1986 by sex and age[6]

Age group (years)*	Population size		
	Male	Female	Total
15 – 19	58,765	57,315	116,080
20 – 24	85,020	87,110	172,130
25 – 29	81,135	81,838	162,973
30 – 34	81,135	81,838	162,973
35 – 39	58,473	62,828	121,300
40 – 44	58,473	62,828	121,300
45 – 49	47,085	51,993	99,078
50 – 54	47,085	51,993	99,078
55 – 59	44,988	53,343	98,330
60 – 64	44,988	53,343	98,330
≥65	83,855	140,495	224,350
Total (15 and over)	691,000	784,920	1,475,920

*Available data summarized using the following age groups: 15–19, 20–24, 25–34, 45–54, 55–59, 60–64, and ≥65. To model 5-year age groups, it was assumed that 50% of each 10-year age group belonged to each of the corresponding 5-year age groups.

Table 6.3.4. Population size and exponential growth factor of the Montréal administrative region over 1986–2020 by sex[3]

	Population size			Growth factor			
Year	**Male**	**Female**	**Total**	**Years**	**Male**	**Female**	**Total**
1986	832,155	920,430	1,752,585	1986 – 1990	0.003	0.002	0.003
1991	846,305	929,565	1,775,870	1991 – 1995	0.004	0.001	0.002
1996	863,685	934,227	1,797,912	1996 – 2000	0.007	0.004	0.006
2001	895,533	954,613	1,850,146	2001 – 2005	0.004	0.001	0.002
2006	915,017	958,008	1,873,025	2006 – 2010	0.005	0.004	0.004
2011	938,707	975,049	1,913,756	2011 – 2015	0.006	0.004	0.005
2016	965,396	993,618	1,959,014	2016 – 2020	0.008	0.005	0.007
2021	1,005,485	1,020,443	2,025,928	-	-	-	-

Exposure category population sizes

Exposure category population size estimates were obtained from various population-based health surveys and are summarized in Table 6.3.5. The main survey, *Enquête Québécoise sur la santé de la population* (EQSP)[10, 11], was implemented in 2008 and 2014–2015 by the ISQ and captured behavioural information on sexual partnerships and drug use for all of Québec, as well as by region. Supplemental sources included *Enquête sur les attitudes et comportements reliés au VIH/sida dans la population générale Québécoise* (EHAQ; 1995–1997)[44] and summarized information from multiple Canadian Health Monitor Surveys (CHMS; 1994, 1995–1996, 1997), as reported by Archibald et al.[12]

Table 6.3.5. Estimates of the MSM and PWID population sizes in Québec and Montréal by sex

Location	Year	Male	Female	Overall	Source
MSM: % of male population aged ≥15 years that had sex with another man in the past 12 months					
Québec	1995-1997	3.4%*	-	-	EHAQ[44]
Québec	2008	2.5% [2.1% had sex only with men; 0.4% had sex with men and women]	-	-	EQSP[11]
Québec	2014-2015	3.4% [2.7% (2.3%–3.2%)† had sex only with men; 0.7% (0.5%–0.9%)† had sex with men and women]	-	-	EQSP[10]
Montréal	1994-1997	1.4%–3.9% [interval mid-point: 2.65%]	-	-	CHMS[12]
Montréal	2008	5.2% [4.7% (2.9%–6.7%)‡ had sex only with men; 0.5% (0.0%–1.1%)‡ had sex with men and women]	-	-	EQSP[11]
Montréal	2014-2015	6.4% [5.6% (4.5%–6.8%)‡ had sex only with men; 0.8% (0.5%–1.4%)‡ had sex with men and women]	-	-	EQSP[10]

Location	Year	Male	Female	Overall	Source
PWID: % of population aged ≥15 years that ever used injection drugs					
Québec	1995-1997	0.8%*	0.2%*	0.5%*	EHAQ[44]
Québec	2008	0.7%	0.2%	0.5%	EQSP[11]
Québec	2014-2015	1.1% (0.9%–1.4%)†	0.5% (0.4%–0.7%)†	0.8% (0.7%–1.0%)†	EQSP[10]
Montréal	1994-1997	Not available	Not available	0.6%–1.8% [interval mid-point: 1.2%]	CHMS[12]
Montréal	2008	0.9% (0.2% – 1.8%)‡	Not available	0.6% (0.20%–1.1%)‡	EQSP[11]
Montréal	2014-2015	1.8% (1.3%–2.5%)‡	0.9% (0.5%–1.3%)†	1.3% (1.0%–1.7%)‡	EQSP[10]

Abbreviations: Enquête sur les attitudes et comportements reliés au VIH/sida dans la population générale Québécoise (EHAQ); Enquête Québécoise sur la santé de la population (EQSP); Canadian Health Monitor Surveys (CHMS).

*% of population aged 15-64 years

†99% confidence interval

‡95% confidence interval

Men who have sex with men

Over 2014-2015, an estimated 3.4% of sexually active men aged ≥15 years had sex with another man in the past 12 months in Québec, with 2.7% (99% CI: 2.3-3.2%) having had sex exclusively with men and 0.7% (99% CI: 0.5-0.9%) having had sex with both men and women[10]. In Montréal, 6.4% of sexually active men aged 15 years and older were estimated to have had sex with another man in the past 12 months, with 5.6% (95% CI: 4.5-6.8%) having had sex only with men and 0.8% (95% CI: 0.5-1.4%) having had sex with both men and women[10]. These proportions were similar to that estimated in the 2008 EQSP[11], as well as the other reports identified[12, 13]. Therefore, we used the 2014-2015 EQSP estimates to model the MSM populations of Québec and Montréal, assuming the proportion of MSM remained constant in time and that all MSM enter the model at 15 years of age.

People who use injection drugs

a. Lifetime injection drug use

The provincial HIV surveillance system attributes an HIV diagnosis to injection drug use (IDU) if the diagnosed individual reports having ever used injection drugs in their lifetime. We correspondingly modeled the population aged ≥15 years who ever used injection drugs over time, thereby, including both active and former PWID in the model.

Few estimates of lifetime IDU for Québec and Montréal were identified, with the earliest in both areas being captured in the mid-1990s (Table 6.3.5). In Québec, the overall and sex-stratified estimates remained consistent over time, with the most recent estimates from the 2014-2015 EQSP suggesting 1.1% (99% CI: 0.9-1.4%) of males and 0.5% (99% CI: 0.4-0.7%) of females aged ≥15 years in Québec ever used injection drugs[10]. In Montréal, few sex-stratified estimates were available prior to the 2014-2015 EQSP, where an estimated 1.8% (95% CI: 1.3 – 2.5%) of males and 0.9% (95% CI: 0.5-1.3%) of females aged ≥15 years reported lifetime IDU[10]. Comparing the overall prevalence of lifetime IDU among those aged ≥15 years in Montréal, however, indicated that the proportion remained stable over time.

Given the paucity of data prior to 1994-1995, as well as sex-stratified estimates for Montréal, and the similarity of the identified estimates over time, we assumed the proportion of lifetime IDU overall and among males and females in Québec and Montréal remained constant at the values determined in 2014-2015[10]. An overall and sex-specific probability distribution for the age of IDU initiation was used to allow PWID to enter the model at each age group. This distribution was informed by data from the SurvUDI network (see Appendix 3), which indicated that over 2005-2008, the mean and standard deviation (SD) of reported age of IDU initiation among active male and female PWID in Québec and the city of Ottawa, Ontario was 23.5 years (SD: 8.5) and 22.6 years (SD: 8.6), respectively[14]. Assuming the number of individuals initiating IDU at each age follows a zero-truncated negative binomial distribution (equations 6.1–6.3), we used the mean and SD values described above to determine the probability of initiation per age group overall and among males and females (Table 6.3.6). We assumed the same probability distribution also applied to PWID in Montréal.

$$Age\ at\ IDU\ initiation\ _{male} \sim ZTNB\left(\text{mean} = 23.5\ , \text{size} = \frac{23.5^2}{8.5^2 - 23.5^2}\right) \quad (6.1)$$

$$Age\ at\ IDU\ initiation\ _{female} \sim ZTNB\left(\text{mean} = 22.6\ , \text{size} = \frac{22.6^2}{8.6^2 - 22.6^2}\right) \quad (6.2)$$

$$Age\ at\ IDU\ initiation\ _{overall} \sim ZTNB\left(\text{mean} = 23.3, \text{size} = \frac{23.3^2}{8.5^2 - 23.3^2}\right) \quad (6.3)$$

Table 6.3.6. Probability of injection drug use initiation by sex and age group for Québec and Montréal, assuming a zero-truncated negative binomial distribution

Age group (years)	Probability		
	Male	Female	Overall
< 15	0.137	0.172	0.143
15–19	0.211	0.223	0.214
20–24	0.239	0.232	0.238
25–29	0.191	0.175	0.188
30–34	0.119	0.105	0.116
35–39	0.061	0.054	0.059
40–44	0.027	0.024	0.026
45–49	0.011	0.010	0.010
50–54	0.004	0.004	0.004
55–59	0.001	0.001	0.001
60–64	0.000	0.000	0.000
≥ 65	0.000	0.000	0.000

b. Active injection drug use

While the entire model captures lifetime IDU, HIV acquisition and IDU-related mortality can only occur among the proportion actively injecting. Available estimates of the active PWID population sizes in Québec and Montréal are in Table 6.3.7.

In Montréal, two data points from 1996 and 2009-2010 are available and indicate the number of active PWID in the city declined from 11,680 to 3,910 people over that period[15, 16]. In the model, we assumed the number of active PWID in Montréal remained constant at 11,680 people over 1975-1996, declined linearly over 1996-2009 according to annual

estimates obtained by linear interpolation, and afterward remained constant at 3,910 people.

In Québec, the earliest estimate from the 1995-1997 EHAQ survey[44] cannot be considered reliable due to the small number of reported active PWID in the sample. Therefore, only data from more recent years (2011-2016) can inform the population of active PWID in the province. To approximate the Québec active PWID population size before 2011, we triangulated the Montréal data to determine the proportion of lifetime PWID active in 1996 (59.7%). We assumed the same proportion applied to the 1996 population of lifetime PWID in Québec, resulting in 28,017 active PWID. As done in Montréal, we assumed the active PWID population size in Québec was constant at 28,017 people over 1975-1996 and performed linear interpolation to approximate the population decline to 11,300 people over 1996-2011[17], following which we used the available data points. Finally, the 2016 estimate of 14,900 people was assumed constant over 2016-2020.

In Montréal and Québec, we assumed the proportion of the active PWID population that were male and female was constant over time at 0.721 and 0.279, respectively, consistent with the 2009-2010 sex-stratified Montréal estimate. Figure 6.3.1 displays the assumed population size of active PWID in Montréal and Québec over time.

Table 6.3.7. Estimated size of the active PWID population aged 15-64 years in Montréal and Québec by sex

Location	Year	Male	Female	Overall	Source
Québec	1995-1997	0.1%	0.06%	0.1%	EHAQ[44]
Québec	2011	Not available	Not available	11,300 (10,000-12,500)*	Jacka[17]
Québec	2012	Not available	Not available	12,300 (10,900-13,700)*	Jacka[17]
Québec	2013	Not available	Not available	13,900 (12,300-15,500)*	Jacka[17]
Québec	2014	Not available	Not available	13,700 (12,200-15,300)*	Jacka[17]
Québec	2015	Not available	Not available	14,700 (13,000-16,400)*	Jacka[17]
Québec	2016	Not available	Not available	14,900 (13,200-16,600)*	Jacka[17]

Location	Year	Male	Female	Overall	Source
Montréal	1996	Not available	Not available	11,680 (8,640-16,460)†	Remis et al.[15], as reported by Archibald et al.[12]
Montréal	2009-2010	2,820 (2,300-3,540)†	1,090 (810-1,500)†	3,910 (3,180 – 4,900)†	Leclerc[16]

*Range of the estimated population size

†95% confidence interval

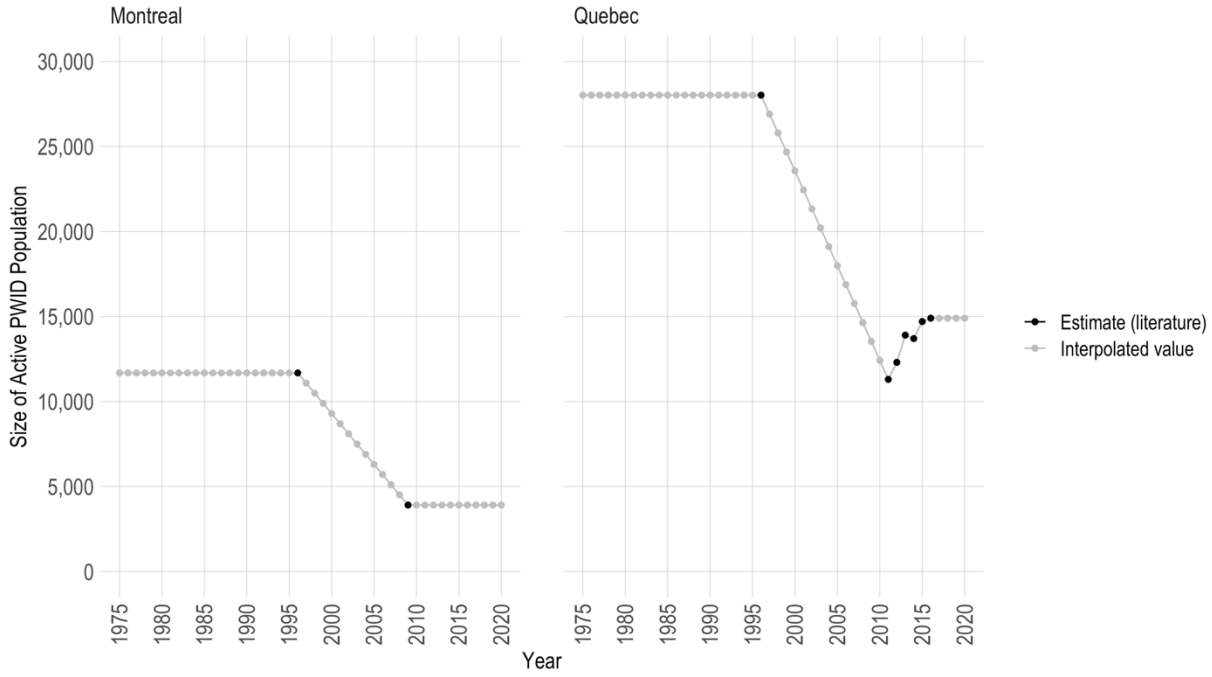


Figure 6.3.1. Modeled active PWID population size aged ≥15 in Montréal and Québec over 1975-2020

Summary

Table 6.3.8 summarizes the proportion of the population assumed to belong to each exposure category and used to establish the model populations.

Table 6.3.8. Proportion of the population ≥15 years assumed to belong to each exposure category over time by sex in Québec and Montréal

Exposure category	Sex	Estimated proportion		Source
		Québec	Montréal	
MSM	Male	3.4%	6.4%	EQSP, 2014-2015[10]
PWID	Male	1.1%	1.8%	EQSP, 2014-2015[10]
	Female	0.5%	0.9%	
	Overall	0.8%	1.3%	

Mortality

Individuals can exit the model due to all-cause or AIDS-related mortality. Mortality data from vital statistics[18] and population data from Statistics Canada[3] were used to calculate annual age-specific all-cause mortality rates for Québec (Figure 6.3.2). Among PWID, the all-cause mortality rates additionally included a weighted IDU-related mortality rate to reflect the increased mortality observed among active PWID[19] (see IDU-related mortality below). PLHIV can also experience AIDS-related mortality (Table 6.3.9).

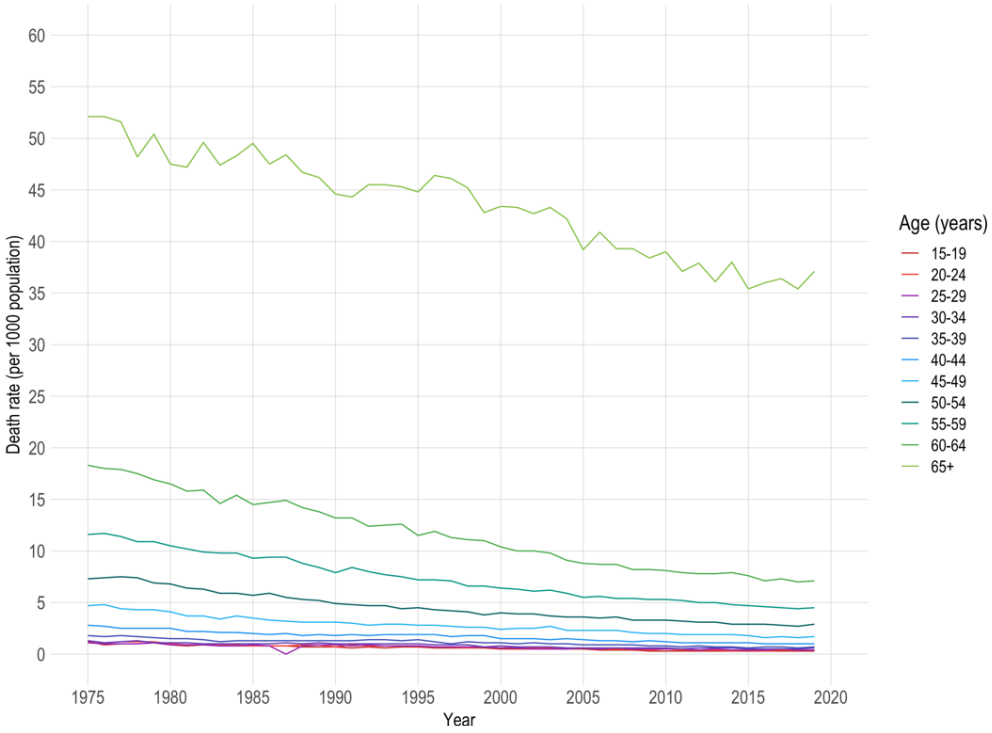


Figure 6.3.2. All cause-mortality rates for Québec by age group

IDU-related mortality

Compared to those who do not use injection drugs, active PWID have a higher risk of death[19]. A previous systematic review determined that active PWID experience a crude all-cause mortality rate of 2.35 deaths per 100 person–years (95% CI: 2.12–2.58), with drug overdose being a leading cause of death[19]. Since our model captures both active and former PWID, we weighted this rate by the proportion of active PWID in the model population at each iteration.

6.3.3. Appendix 3

Model parameterization

Table 6.3.9. Model parameter values and prior distributions used to estimate HIV incidence among MSM, PWID, and heterosexual populations in Montréal and Québec

Parameter	Symbol*	Unit	Value, range, or prior distribution	Source
		Demography		
Population growth rate	$\zeta_j(t)$	year^{-1}	See Table 6.3.2 and Table 6.3.4	Census[4-7] and population estimates[3, 8]
Background mortality rate	$\mu_i(t)$	year^{-1}	See Figure 6.3.2	Vital statistics[18] and population estimates[3]
IDU-related mortality rate	$\mu_{IDU}(t)$	1000 person-years^{-1}	23.5†	Mathers[19]
Population recruitment size	$\alpha_{ij}(t)$	people	$\theta_j(t-1) + \zeta_j(t) * N_j(t-1)$, where $\theta_j(t-1)$ and $N_j(t-1)$ are the total number of deaths and the population size in the model at time $t-1$, respectively.	See Section 2
Proportion of HIV-susceptible population at-risk due to sexual activity or active IDU	$\delta_j(t)$	-	MSM: 1.0 PWID: see Figure 6.3.1	See Section 2
		Natural history		

Parameter	Symbol*	Unit	Value, range, or prior distribution	Source
HIV incidence rate‡	$\lambda_{ij}(t)$	year^{-1}	When estimating incidence overall: $b_{j_1} = 0$ $b_{j_{2,3}} \sim logit^{-1}\big(N(1, 1.5)\big) * 0.25$ $b_{j_n} \sim logit^{-1}\big(N(-1, 1.5)\big) * 0.15$, for $n \in [4, m + 3]$ When estimating incidence by age: $b_{j_{2,3}} \sim logit^{-1}\big(N(0, 1.55)\big) * \big(\mathrm{b}_{2,3} - \mathrm{a}_{2,3}\big) + \mathrm{a}_{2,3}$ $b_{j_n} \sim logit^{-1}\big(N(0, 1.55)\big) * (\mathrm{b}_n - \mathrm{a}_n) + \mathrm{a}_n$, for $n \in [4, m + 3]$ $u_{ij_n} \sim N(0, 0.2)$	Calibration
Duration of primary infection	$1/\rho_p$	year	0.242	Hollingsworth[20]
Disease progression rate (in absence of ART)§	ρ_k	year^{-1}	ρ_1 = 1/3.32 ρ_2 = 1/2.70 ρ_3 = 1/5.50 ρ_4 = 1/5.06	Cori[21]
Proportion of primary infection subsequently allocated to each disease stage	f_k	N/A	f_1 = 0.76 f_2 = 0.19 f_3 = 0.05 f_4 = 0.00	Cori[21]
Diagnostic and treatment rates				
Testing rates¶	$\tau_{jk}(t)$	year^{-1}	$s_{k = S,1,2,3} \sim logit^{-1}\big(N(0, 1.55)\big) * (0.5 - 0.05) + 0.05$ $s_{k = 4} \sim logit^{-1}\big(N(0, 1.55)\big) * (0.75 - 0.25) + 0.25$ $c_{k = S,1,2,3} = 2000$ $c_{k = 4} = 1985$ $l_S = 1.65$ for MSM $l_S \sim logit^{-1}\big(N(0, 1.55)\big) * (2 - 0.05) + 0.05$ for PWID	Calibration

Parameter	Symbol*	Unit	Value, range, or prior distribution	Source
			$l_{k=1,2,3} \sim logit^{-1}\big(N(0, 1.55)\big) * (2 - 0.05) + 0.05$ $l_{k=4} = 8$	
Proportion of AIDS diagnoses reported	$\phi_A(t)$	-	MSM: 0.85 for $t \in [1975, 1996]$, 0.75 for $t \in [1997, 2002]$ PWID: 0.75 for $t \in [1975, 2002]$	Remis[22], assumption
Proportion of new HIV diagnoses reported#	$\phi_H(t)$	-	$\sim logit^{-1}\big(N(0, 1.55)\big) * (1 - 0.6) + 0.6$ for $t \in [2003, 2011]$ $\sim logit^{-1}\big(N(0, 1.55)\big) * (1 - 0.6) + 0.6$ for $t \geq 2012$	Calibration
ART treatment rate	$\gamma_k(t)$	year^{-1}	MSM: $\gamma_{3,4}(t) = \begin{cases} 0, & t < 1996 \\ \frac{1}{2.06}, & t \in [1996, 2003) \\ \frac{1}{0.40}, & t \in [2003, 2012) \\ \frac{1}{0.08}, & t \geq 2013 \end{cases}$ $\gamma_2(t) = \begin{cases} 0, & t < 2013 \\ \frac{1}{0.08}, & t \geq 2013 \end{cases}$ $\gamma_1(t) = \begin{cases} 0, & t < 2015 \\ \frac{1}{0.08}, & t \geq 2015 \end{cases}$ PWID: $\gamma_{3,4}(t) = \begin{cases} 0, & t < 1996 \\ \frac{1}{4.12}, & t \in [1996, 2003) \\ \frac{1}{0.80}, & t \in [2003, 2012) \\ \frac{1}{0.16}, & t \geq 2013 \end{cases}$	Assumption**

Parameter	Symbol*	Unit	Value, range, or prior distribution	Source
			$\gamma_2(t) = \begin{cases} 0, & \mathrm{t} < 2013 \\ \frac{1}{0.16}, & \mathrm{t} \geq 2013 \end{cases}$	
			$\gamma_1(t) = \begin{cases} 0, & \mathrm{t} < 2015 \\ \frac{1}{0.16}, & \mathrm{t} \geq 2015 \end{cases}$	

Abbreviations: injection drug use (IDU); men who have sex with men (MSM); people who inject drugs (PWID); antiretroviral therapy (ART).

*The symbol *t* indicates time. Index *i* indicates age group (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+), *j* indicates sex (male, female), and *k* indicates disease stage (S=susceptible; 1=CD4 >500 cells/μL; 2=CD4 350-500 cells/μL; 3=CD4 200-349 cells/μL; and 4=CD4 <200 cells/μL).

†Only applicable to the PWID model and weighted by the proportion of active PWID in the model population over time. See Section 2 for more detail.

‡Modeled by a cubic M-spline with m internal knots and $n = m + 3$ coefficients $\beta_{ij_n} = e^{log(b_{j_n}) + u_{ij_n}} \geq 0$, where $u_{ij_n} = 0$ when estimating incidence overall, rather than varied by age (see Section 3 for more detail). To estimate incidence by age, an empirical Bayes approach was taken and the priors for the coefficients β_{ij_n} were narrowed to that of the posterior range $(\mathrm{a}_n, \mathrm{b}_n)$ of the coefficients when estimated overall.

§ρ_4 corresponds to the AIDS-related mortality rate.

¶Modeled by logistic growth curves with scale (*s*), midpoint (*c*), and limiting (*l*) parameters such that the testing rate at time *t* is calculated as $\tau_{jk}(t) = \frac{l_k}{1 + e^{-s_k * (t - c_k)}}$. For MSM, l_S was estimated from the RDS-adjusted annual testing rate of the Engage Study (see Section 3). All other fixed values or distribution parameters were assumed.

#For simplicity, we assumed reporting was uncorrelated with age or CD4 count.

**For MSM, the time-varying ART initiation rates for $\gamma_{3,4}(t)$ over $\mathrm{t} \in [1996, 2003)$ and $\mathrm{t} \in [2003, 2012)$ were calculated from the Argus I and Engage studies (see Section 3) and were assumed from 2013 onward. For PWID, we assumed the time to ART initiation was twice that among MSM.

Data sources

Peer-reviewed literature and data from three local studies were used to inform the model parameters. Key features of these studies and the parameters they informed are summarized in Table 6.3.10. Sources for all other input parameters are provided in Table 6.3.9.

Table 6.3.10. Local data sources used to inform MSM and PWID model parameters

Study	Population	Location	Year (N)	Design	Sample type	Parameters
Argus[23-25]	MSM	Montréal	2005-2007 (1,957); 2008-2009 (1,873)	Repeated cross-sectional	Convenience (modified time-location sampling)	ART initiation rate
Engage[26]	MSM	Montréal	2017-2018 (1,179)	Cohort	Respondent driven sampling	HIV testing rate, ART initiation rate
SurvUDI[27, 28]	PWID	Québec and Ottawa, Ontario	1995 – present (15,200)	Repeated cross-sectional	Convenience	Model entry (age at IDU initiation)

Abbreviations: men who have sex with men (MSM); antiretroviral treatment (ART); people who use injection drugs (PWID); injection drug use (IDU).

Men who have sex with men

Data from two studies of Montréal MSM were used to inform the model parameters. The first, Argus, was a repeated cross-sectional survey with two cycles over 2005-2007 (Argus I, N=1,957)[23, 24] and 2008-2009 (Argus II, N=1,873)[25]. At each cycle, MSM aged ≥18 years were recruited into the study at various community venues using a modified time-location sampling method. The second study, Engage, is an ongoing prospective cohort study of MSM aged ≥16 years in Montréal, Toronto, and Vancouver. For these purposes, we used the baseline data of the Montréal participants (N=1,179), recruited over 2017-2018[26] by respondent-driven sampling (RDS), constituting a more representative sample of Montréal MSM. To account for the convenience sampling used in Argus, the data were standardized to the Engage study based on age and ethnicity (Canadian-born vs. elsewhere).

Together, these surveys informed the HIV testing rate among HIV-negative MSM and the time-varying ART initiation rates among PLHIV. Specifically, the annual testing rate

among HIV-negative participants was calculated and adjusted using RDS-II weights to account for the sampling strategy. The resulting estimate was assumed to be the limiting value of the logistic growth curve used to model the testing rate among those susceptible to HIV acquisition (l_S). To determine the ART initiation rates ($\gamma_k(t)$), we used Poisson regression to estimate the mean duration from HIV diagnosis to first use of ART among men aware they were living with HIV in the Argus I (those diagnosed over 1996-2005) and Engage (those diagnosed after 2005) studies. We stratified the estimate by period (1997-2003 and 2004-2013) to allow the parameter value to time-vary. We again adjusted for the sampling method by applying RDS-II weights to the Engage participants and standardization weights to those from Argus I.

People who inject drugs

Among PWID, we used reported information from the SurvUDI network to inform the age at IDU initiation (as described above in *Model demography*). SurvUDI is an ongoing, repeated cross-sectional surveillance study of active PWID that has been conducted annually since 1995 across regions of Québec and the city of Ottawa, Ontario[27, 28]. By the end of March 2018, N=15,200 unique PWID aged ≥14 years that used drugs in the past six months were recruited into the study from various sites frequented by active PWID, including needle exchange program sites (constituting around 90% of the recruitment), rehabilitation centers, detention centers and shelters[28]. Individuals could participate in the study multiple times and at any location, with a minimum period of at least six months between visits.

Incidence spline

The time-varying HIV incidence rate was flexibly modeled over 1975–2020 by a cubic M-spline[2, 29], a continuous function of non-negative piecewise polynomials joining together at m internal knot points $\upsilon_1 < \cdots < \upsilon_m$. Let *t* indicate time, *i* age, *j* sex, *p* the polynomial degree (where *p*=3 corresponds to cubic polynomials), β_{ij_n} the spline coefficients, and M(t) the M-spline basis[29]. The HIV incidence curve over time, $\lambda_{ij}(t)$, is as formulated in equation 7.0:

$$\lambda_{ij}(t) = \sum_{n=1}^{m+p} \beta_{ij_n} * \mathrm{M(t)} \qquad (7.0),$$

where $\beta_{ij_n} = e^{log(b_{j_n})+u_{ij_n}}$ and $u_{ij_n} = 0$ when modeling incidence overall, rather than by age.

The R package *splines2*[30] was used to formulate M(t) in our model. The first spline coefficient β_{ij_1} was set to 0 so that incidence would begin at 0 in 1975. The remaining coefficients, which are constrained to be positive, were obtained by estimating b_i and u_{ij} (when estimating incidence by age) in model calibration on the log-scale. The number and location of knots was varied to determine the best fitting incidence curve. Three scenarios of knot placements were explored (Table 6.3.11): 1) equidistant knots; 2) knots focused earlier in the epidemic, where increased flexibility might be needed; and 3) knots focused where more data is available. The model resulting in the lowest Watanabe–Akaike information criterion (WAIC) or leave-one-out information criteria (LOOIC) was selected as the final model.

Table 6.3.11. Incidence M-spline scenarios for knot placement

N knots	Knot locations		
	1. Equally spaced	**2. Focused where increased flexibility needed**	**3. Focused where more available data**
3	1986.3, 1997.5, 2008.8	1985, 1996, 2000	1997, 2003, 2007
4	1984, 1993, 2002, 2011	1985, 1990, 1996, 2000	1997, 2003, 2007, 2010
5	1982.5, 1990.0, 1997.5, 2005.0, 2012.5	1980, 1985, 1990, 1996, 2000	1997, 2003, 2007, 2010, 2014
6	1981.4, 1987.9, 1994.3, 2000.7, 2007.1, 2013.6	1980, 1985, 1990, 1996, 2000, 2007	1997, 2003, 2007, 2010, 2014, 2018
7	1980.6, 1986.3, 1991.9, 1997.5, 2003.1, 2008.8, 2014.4	1980, 1985, 1990, 1996, 2000, 2007, 2014	1985, 1997, 2003, 2007, 2010, 2014, 2018

6.3.4. Appendix 4

Model calibration and cross-validation

Calibration and cross-validation outcomes

Model calibration is performed to estimate values of the unknown parameters. This involves comparing the model outcomes to independent, empirical data points to obtain the set of parameter values that best fit the data and match the epidemic trends[33, 34]. Table 6.3.12 details the outcomes used for model calibration and cross-validation. The main calibration data source was provincial surveillance data from *l'Institut national de santé publique du Québec* (INSPQ). At the beginning of the epidemic, only AIDS cases were collected by Québec's surveillance program[35, 36]. While the reporting of AIDS cases continued until 2002, the availability of ART in 1997 led to a subsequent reduction in the number of PLHIV advancing to the AIDS stage and a greater uncertainty in the completeness of reporting after that time. Part way through 2002, HIV came under surveillance in Québec, becoming reportable by the provincial laboratories responsible for carrying out tests, along with some relevant epidemiological data[36, 37]. Correspondingly, the INSPQ data utilized includes the annual number of AIDS cases over 1979-1998 and the annual number of HIV diagnoses from 2003-2020. The AIDS data is stratified by exposure category and sex. The HIV diagnosis data is stratified by exposure category, sex, age, and self-reported time since last negative HIV test (2003-2020). More recently, HIV diagnoses are also stratified by CD4 cell count at new diagnosis (2013-2020).

Data from the Argus surveys and the Engage study were used as cross-validation outcomes for Montréal MSM. Again, Argus survey estimates were standardized to the Engage study. Among PWID, there were no comparable data for cross-validation (SurvUDI estimates do not apply due to differences in the population, i.e. active vs. lifetime PWID).

Table 6.3.12. Outcomes used for model calibration and cross-validation

Outcomes	Time range	Data sources
Calibration		
AIDS diagnoses (overall and by sex)	1979-2002	INSPQ[35, 36]
New HIV diagnoses (overall and by sex and age)	2003-2020*	INSPQ

Outcomes	Time range	Data sources
New HIV diagnoses by CD4 cell count at diagnosis (overall and by sex and age)[†]	2013-2020[*]	INSPQ
Proportion of new diagnoses recently tested (P12M; overall and by sex and age)[‡]	2003-2020[*]	INSPQ
Cross-validation		
HIV prevalence	2005-2007 (Argus I) 2008-2010 (Argus II) 2017-2018 (Engage)	Argus (Montréal) Engage (Montréal)[26]
Percentage of PLHIV undiagnosed	2017 – 2018 (Engage)	Engage (Montréal)[26, 38]
Percentage of diagnosed PLHIV that initiated ART	2005 – 2007 (Argus I) 2008 – 2010 (Argus II) 2017 – 2018 (Engage)	Argus (Montréal) Engage (Montréal)

Abbreviations: Institut national de santé publique du Québec (INSPQ); past 12 months (P12M); people living with HIV (PLHIV); antiretroviral treatment (ART).

[*]Due to the COVID-19 pandemic, the data from 2020 were excluded from model calibration in the main analyses and included in sensitivity analyses.

[†]The CD4 cell count contained missing values. These were assumed to be missing completely at random.

[‡]The testing data is categorized as *never previously tested*, *unsure when last tested*, *tested <12 months ago*, and *tested ≥12 months ago*. In calculating the proportion of new diagnoses recently tested, it is assumed that those reporting as *unsure when last tested* (<4% of observations) did not test in the past 12 months.

Calibration method: optimization

The calibration of our model was carried out using optimization under a Bayesian framework, allowing uncertainty in the estimated parameters to be reflected in the model's predictions and ensuring identifiability of the unknown parameters given the number of degrees of freedom. Maximum a posteriori estimation (MAP), a Bayesian analog of maximum likelihood estimation that maximizes the joint posterior probability, can obtain estimators of unknown parameters in such optimization problems[39]. We specifically obtained the MAP parameter point estimates by minimizing the negative posterior log-

likelihood of the model. The prior distributions placed over the unknown parameters are as formulated in Table 6.3.9. The model posterior likelihood is described below. As optimization searches over the entire set of real numbers for all parameters, we logit transformed and scaled the optimized values to ensure all parameter estimates were on the appropriate scale and within relevant bounds, as needed.

A two-step optimization method was performed. First, we used the Nelder-Mead algorithm with starting values randomly selected from the parameter prior distributions and a maximum of 10,000 iterations. We then used the BFGS algorithm, starting from the Nelder-Mead optimized parameter values and continuing to convergence. Secondly, we used sampling importance resampling (SIR) to approximate the posterior distribution, taking the final BFGS optimized parameter values as the posterior mode. The initial samples (n=50,000) from the posterior distribution were drawn from a multivariate *t*-distribution, using the estimated hessian matrix as the scale matrix. Using standardized importance weights as sampling probabilities, 1000 resamples were then taken without replacement, as suggested by Gelman et al.[40] to be appropriate when few of the resulting importance weights are large. Posterior distributions are summarized by the median and the 2.5th and 97.5th percentiles estimated 95% credible intervals.

Model posterior likelihood

Let θ be the vector of model parameters. For each time *t* (specific to each outcome), age group *i*, and sex *j*, let $D_{t,j,i}$ correspond to outcomes observed in the data and $M_{t,j,i}$ correspond to outcomes predicted by the model.

Number of reported AIDS cases

The observed number of reported AIDS cases, $D_{t,j}^{AIDS}$, a cumulative count over 1975-1998, followed a negative binomial distribution with mean and variance:

$$E\left[D_{t,j}^{AIDS}\right] = M_{t,j}^{AIDS} \text{ and } Var\left[D_{t,j}^{AIDS}\right] = M_{t,j}^{AIDS} + \frac{M_{t,j}^{AIDS^2}}{r},$$

where $M_{t,j}^{AIDS}$ is the model-predicted number of AIDS diagnoses and the dispersion parameter, r, was fixed at 100. Reported AIDS cases $\left(D_{t,j}^{AIDS}\right)$, met the clinical case

definition in use at the time of diagnosis[35, 36]. The definition was initially based on the diagnosis of opportunistic infections, changing over time as the list of these infections expanded, and a positive HIV test result when it was added to the case definition in 1985. In the model, we proxy this case definition by defining AIDS cases as individuals with a CD4<200 cells/μL. The annual model-predicted number of AIDS diagnoses $\left(M_{t,j}^{AIDS}\right)$ is taken as the sum of 1) the number of PLHIV that transition from the undiagnosed to diagnosed CD4<200 cells/μL compartment over a calendar year and 2) the number of PLHIV that are diagnosed and transition from the CD4 200-349 cells/μL compartment to the CD4<200 cells/μL compartment.

The observed likelihood function is as follows:

$$\mathcal{L}_{AIDS}\left(\theta \mid D_{t,j}^{AIDS}\right) = \prod_{t}\left(\frac{\Gamma\left(D_{t,j}^{AIDS}+r\right)}{\Gamma\left(D_{t,j}^{AIDS}+1\right)\Gamma(r)}\right)\left(\frac{r}{M_{t,j}^{AIDS}+r}\right)^{r}\left(\frac{M_{t,j}^{AIDS}}{M_{t,j}^{AIDS}+r}\right)^{D_{t,j}^{AIDS}} \quad (9.1)$$

Number of reported new HIV diagnoses

The observed number of reported new HIV diagnoses, $D_{t,i,j}^{HIV}$, for $t \in [2003, \ldots, 2020]$, similarly followed a negative binomial distribution with mean and variance:

$$E\left[D_{t,i,j}^{HIV}\right] = M_{t,i,j}^{HIV} \text{ and } Var\left[D_{t,i,j}^{HIV}\right] = M_{t,i,j}^{HIV} + \frac{M_{t,i,j}^{HIV\,2}}{r},$$

where $M_{t,i,j}^{HIV}$ is the model-predicted number of HIV diagnoses and the dispersion parameter r remained fixed at 100. The observed likelihood function is as follows:

$$\mathcal{L}_{HIV}\left(\theta \mid D_{t,i,j}^{HIV}\right) = \prod_{t}\prod_{i}\left(\frac{\Gamma\left(D_{t,i,j}^{HIV}+r\right)}{\Gamma\left(D_{t,i,j}^{HIV}+1\right)\Gamma(r)}\right)\left(\frac{r}{M_{t,i,j}^{HIV}+r}\right)^{r}\left(\frac{M_{t,i,j}^{HIV}}{M_{t,i,j}^{HIV}+r}\right)^{D_{t,i,j}^{HIV}} \quad (9.2)$$

Proportion of reported new HIV diagnoses that recently tested negative

The observed proportion of reported new HIV diagnoses recently tested negative, $p_{D_{t,i,j}^{test}}$, for $t \in [2003, \ldots, 2020]$, followed a binomial distribution. The observed likelihood is:

$$\mathcal{L}_{test}\left(\theta \mid p_{D_{t,i,j}^{test}}\right) = \prod_{t}\prod_{i}\binom{D_{t,i,j}^{HIV}}{D_{t,i,j}^{test}} p_{M_{t,i,j}^{test}}{}^{D_{t,i,j}^{test}} \left(1 - p_{M_{t,i,j}^{test}}\right)^{D_{t,i,j}^{HIV} - D_{t,i,j}^{test}} \tag{9.3}$$

where $D_{t,i,j}^{test}$ indicates the observed number of reported new HIV diagnoses that received a negative HIV test in the past 12 months and $p_{M_{t,i,j}^{test}} = M_{t,i,j}^{test} / M_{t,i,j}^{HIV}$ is the model-predicted proportion of reported new HIV diagnoses that tested negative in the past 18 months. $M_{t,i,j}^{test}$, the model-predicted number of new HIV diagnoses that tested negative in the past 18 months, is determined using compartments that specifically track HIV testing histories (Figure 6.3.3).

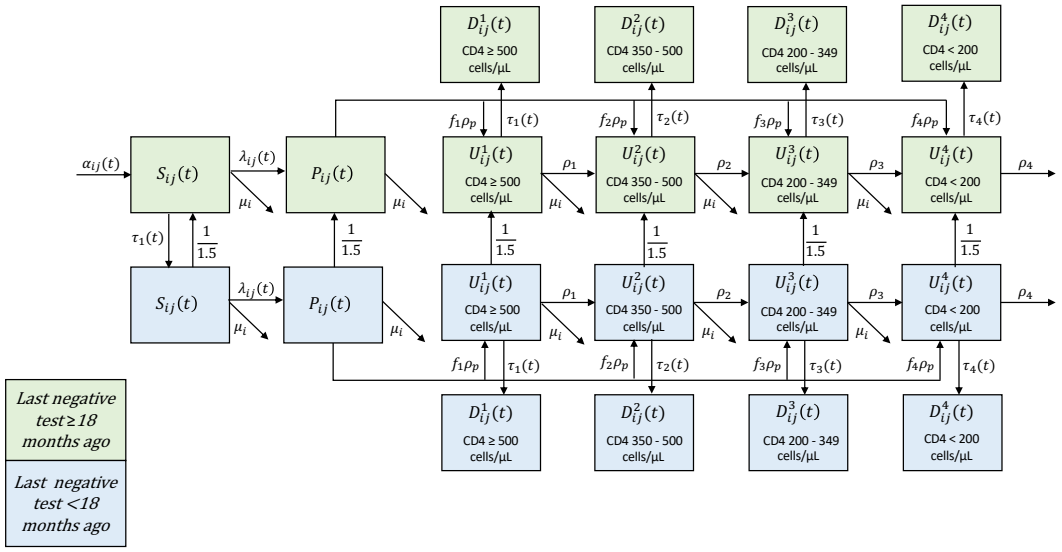


Figure 6.3.3. Diagram of the main inter-compartmental flows for HIV testing histories

The index *i* indicates age group (15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65+), *j* indicates sex (male, female), and *k* indicates disease stage (1=CD4≥500 cells/μL; 2=CD4 350-499 cells/μL; 3=CD4 200-349 cells/μL; and 4=CD4<200 cells/μL). Susceptible individuals that do not acquire HIV can transition into the recently tested negative (<18 months ago) and susceptible compartment at the rate $\tau_1(t)$. Those individuals can progress back into the not recently tested negative compartments (≥18 months ago) via the susceptible, primary infection, and undiagnosed compartments at a rate of 1/1.5 years^{-1}.

Number of reported new HIV diagnoses by CD4 cell count

The observed number of new HIV diagnoses per CD4 cell count category $D^{CD4}_{t,i,j,k}$, for $t \in [2013, \dots, 2020]$ and $k \in [1, 2, 3, 4]$, follows a multinomial distribution. The observed likelihood is as follows:

$$\mathcal{L}_{CD4}\left(\theta \mid D^{CD4}_{t,i,j,k=1}, \dots, D^{CD4}_{t,i,j,k=4}\right) = \prod_t \prod_i \frac{N^{CD4}_{t,i,j}}{D^{CD4}_{t,i,j,k=1}! \cdots D^{CD4}_{t,i,j,k=4}!} \prod_k p^{M^{CD4}_{t,i,j,k}}_{t,i,j,k} \qquad (9.4)\,,$$

where $N^{CD4}_{t,i,j} = \sum_k D^{CD4}_{t,i,j,k}$ and $p^{M^{CD4}_{t,i,j,k}}_{t,i,j,k}$ is the model-predicted proportion of reported new HIV diagnoses per CD4 cell count category.

The overall model posterior likelihood is then taken as the prior likelihood multiplied by the likelihood of all data.

6.3.5. Appendix 5

Final models

Attributes of the modeled incidence M-spline

Table 6.3.13. Number and placement of knots included in incidence M-spline of final models

Location	Sex	N knots	Knot location
Men who have sex with men			
Montréal[*]	Male	4	1984, 1993, 2002, 2011 (equally spaced)[†]
Province of Québec[*]	Male	4	1985, 1990, 1996, 2000 (focused where increased flexibility needed)
People who inject drugs (includes active and past injectors)			
Montréal	Overall	3	1997, 2003, 2007 (focused where more available data)
Montréal	Male	3	1985, 1996, 2000 (focused where increased flexibility needed)
Montréal	Female	4	1985, 1990, 1996, 2000 (focused where increased flexibility needed)
Province of Québec	Overall	4	1984, 1993, 2002, 2011 (equally spaced)
Province of Québec	Male	3	1986.3, 1997.5, 2008.8 (equally spaced)

Province of Québec	Female	3	1997, 2003, 2007 (focused where more available data)

*The same number and placement of knots was used when estimating incidence by age.

†The final models were selected considering both the WAIC and LOOIC.

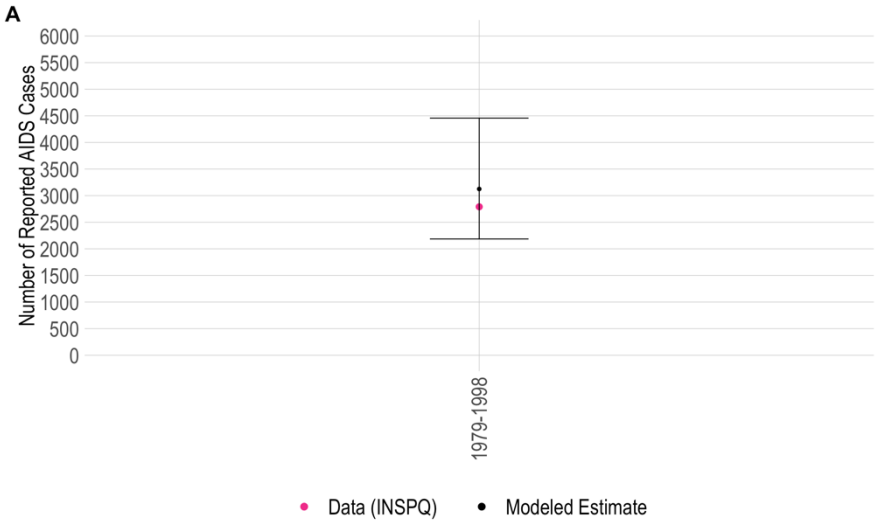
Sensitivity analyses

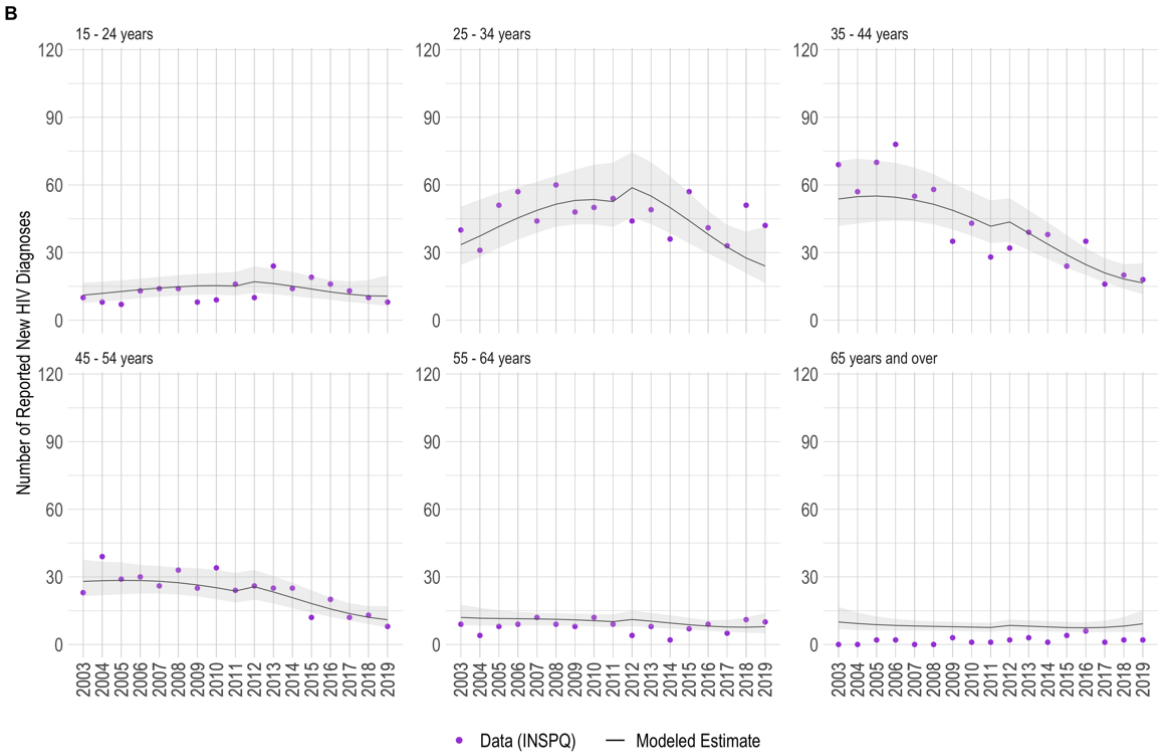
We assessed the sensitivity of the model to some of the assumed parameter inputs. First, we varied the assumed ART initiation rates among PWID, as empirical information to inform parameters was not available. We further allowed the ART initiation rates to vary between the treatment-eligible CD4 cell count categories over 1996-2013, setting the 1996-2012 ART initiation rates among those with CD4 350-200 cells/μL equal to 0.75 and 0.5 times that of those with CD4 <200 cells/μL. From 2013 onward, we maintained the assumption of equal rates across categories since treatment initiation is rapid from then on. Lastly, we assessed alternate disease progression parameters available in the literature to ensure the chosen inputs did not impact the results. In all, we found that our model was not very sensitive to these assumptions, as none of the results were meaningfully impacted by these changes.

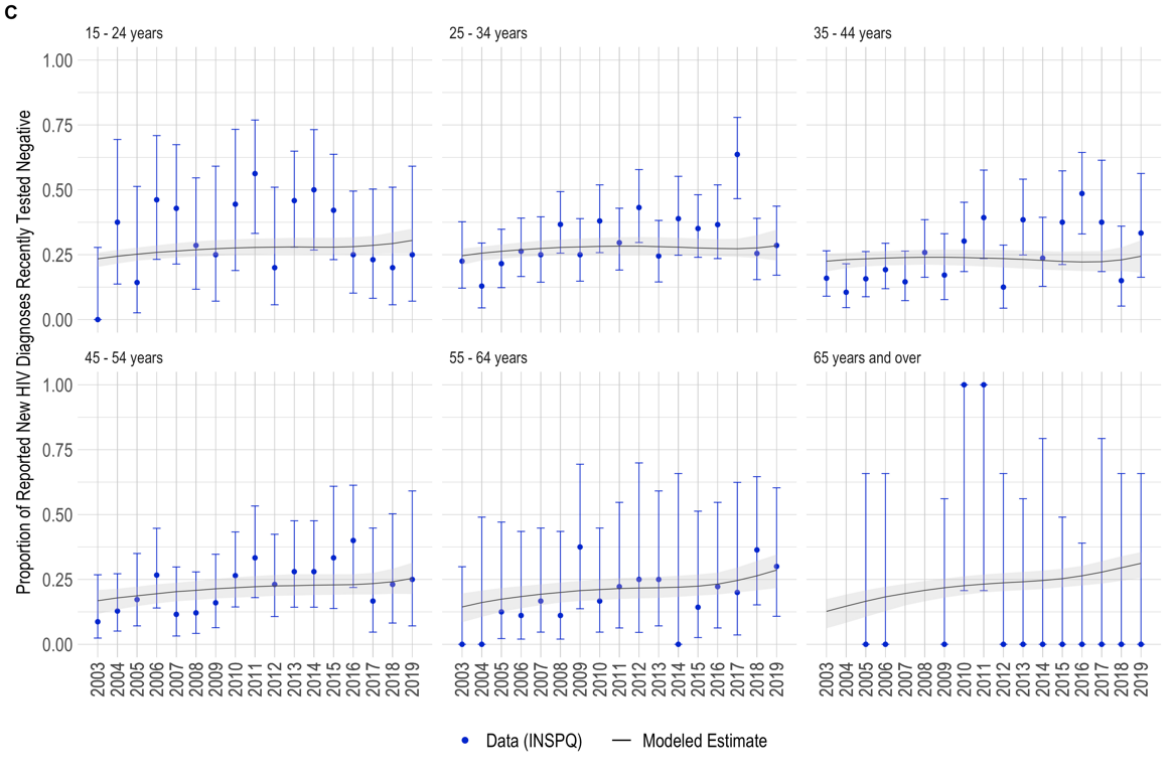
6.3.6. Appendix 6

Additional figures of model fits (calibration outcomes)

Men who have sex with men




B
15 - 24 years
25 - 34 years
35 - 44 years
45 - 54 years
55 - 64 years
65 years and over
Number of Reported New HIV Diagnoses
0
30
60
90
120
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Data (INSPQ)
Modeled Estimate


C
15 - 24 years
25 - 34 years
35 - 44 years
45 - 54 years
55 - 64 years
65 years and over
Proportion of Reported New HIV Diagnoses Recently Tested Negative
0.00
0.25
0.50
0.75
1.00
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Data (INSPQ)
Modeled Estimate

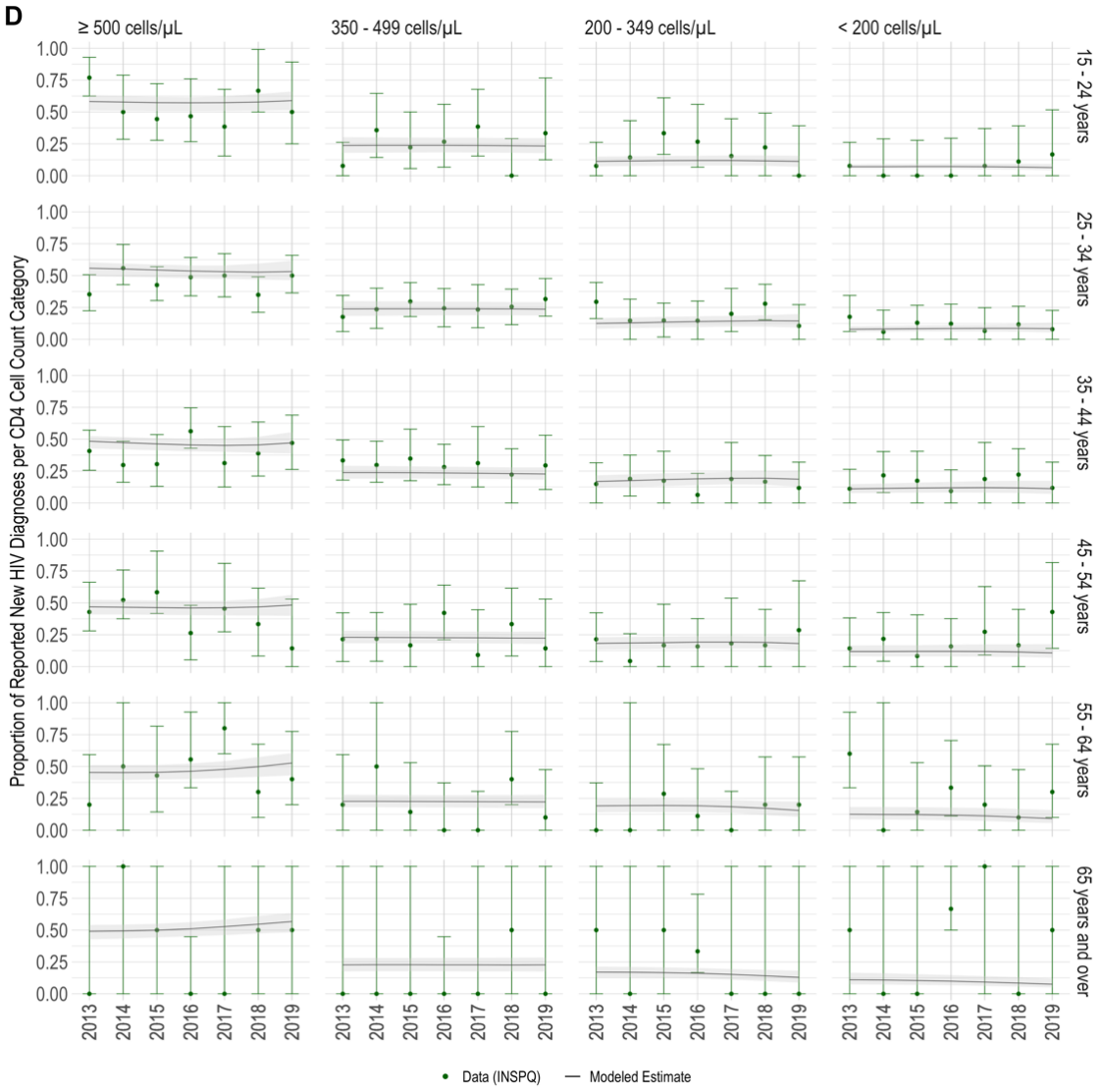
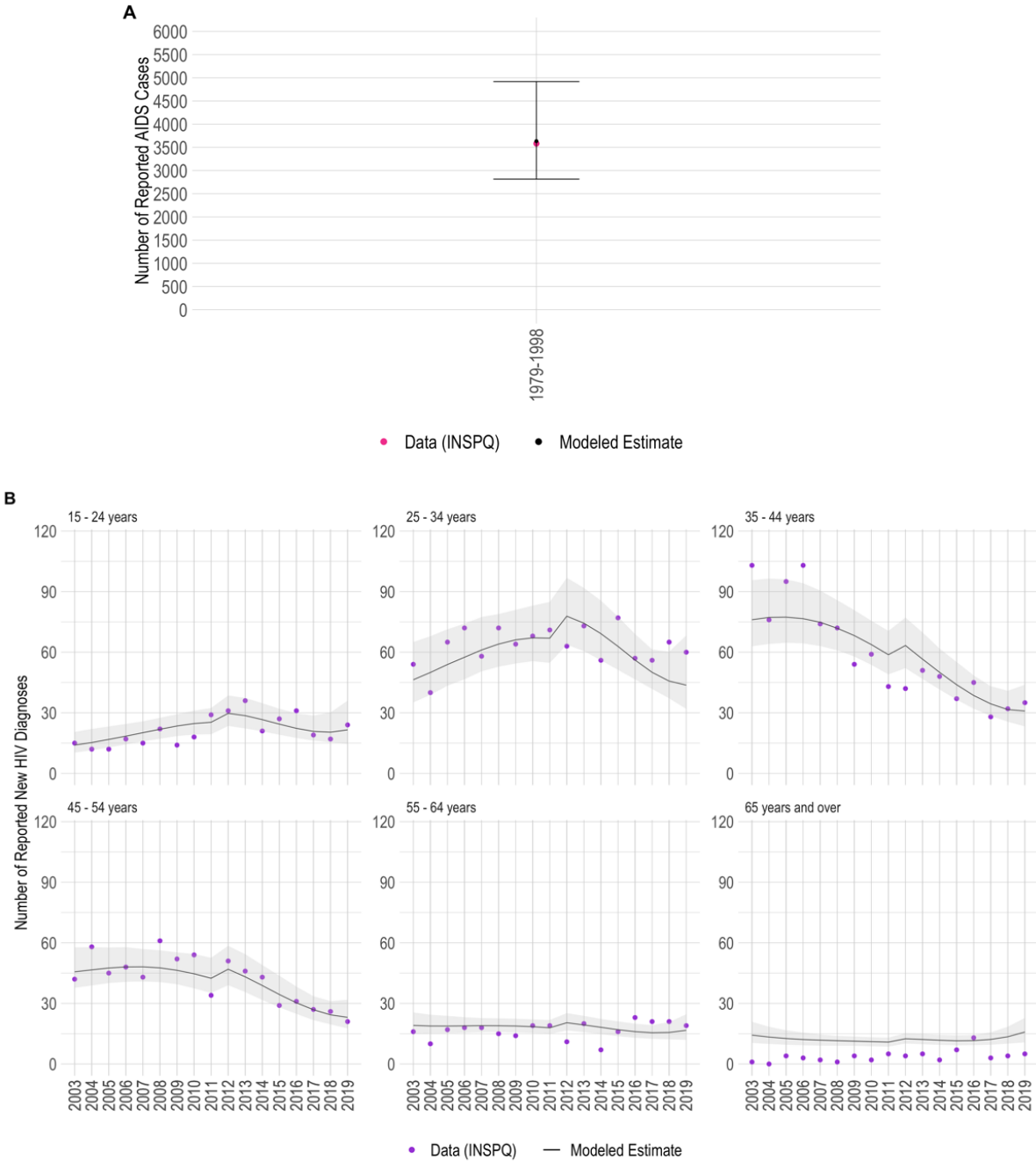
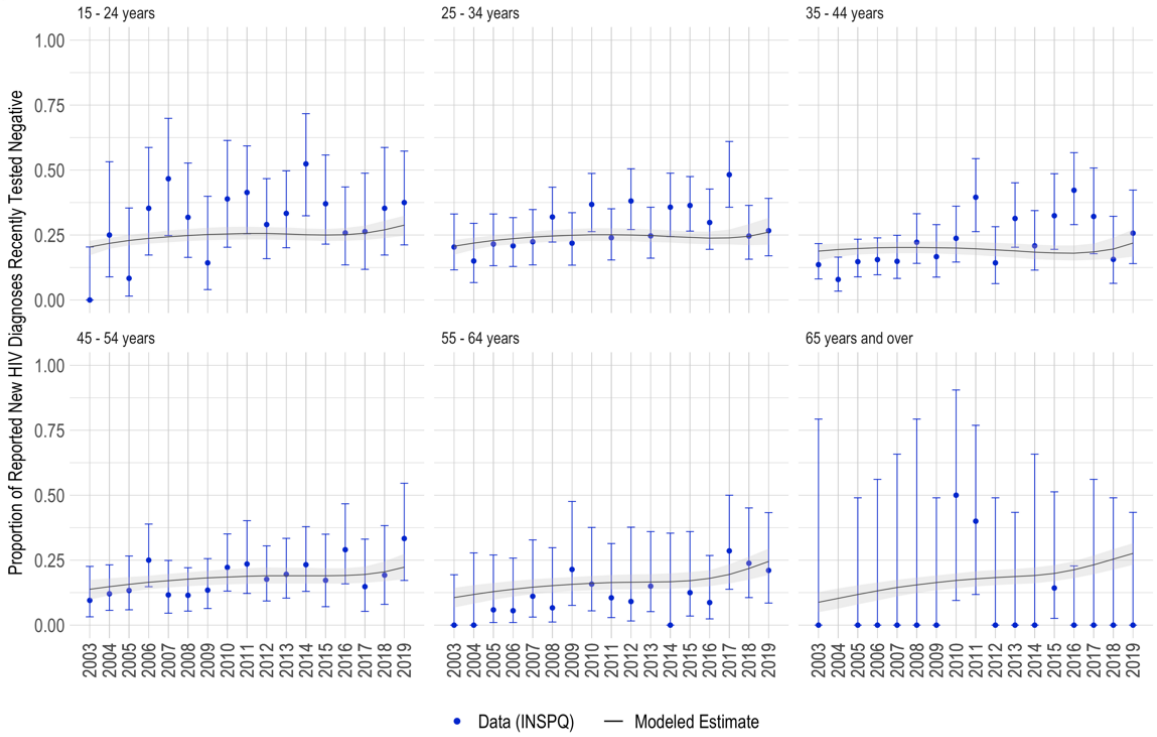


Figure 6.3.4. Model fits among men who have sex with men in Montréal

Model fits to the age-stratified calibration outcomes among men who have sex with men in Montréal: A) number of reported AIDS cases; B) number of reported new HIV diagnoses by age group; C) proportion of reported new HIV diagnoses that recently tested negative by age group; and D) proportion of reported new HIV diagnoses per CD4 cell count category and age group. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The coloured points and bars display the outcomes from the *Institut national de santé publique du Québec* (INSPQ) data and their corresponding 95% confidence intervals, where applicable.


A
Number of Reported AIDS Cases
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1979-1998
Data (INSPQ)
Modeled Estimate
B
Number of Reported New HIV Diagnoses
15 - 24 years
25 - 34 years
35 - 44 years
45 - 54 years
55 - 64 years
65 years and over
120
90
60
30
0
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Data (INSPQ)
Modeled Estimate

C


15 - 24 years
25 - 34 years
35 - 44 years
45 - 54 years
55 - 64 years
65 years and over
Proportion of Reported New HIV Diagnoses Recently Tested Negative
1.00
0.75
0.50
0.25
0.00
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
Data (INSPQ)
Modeled Estimate

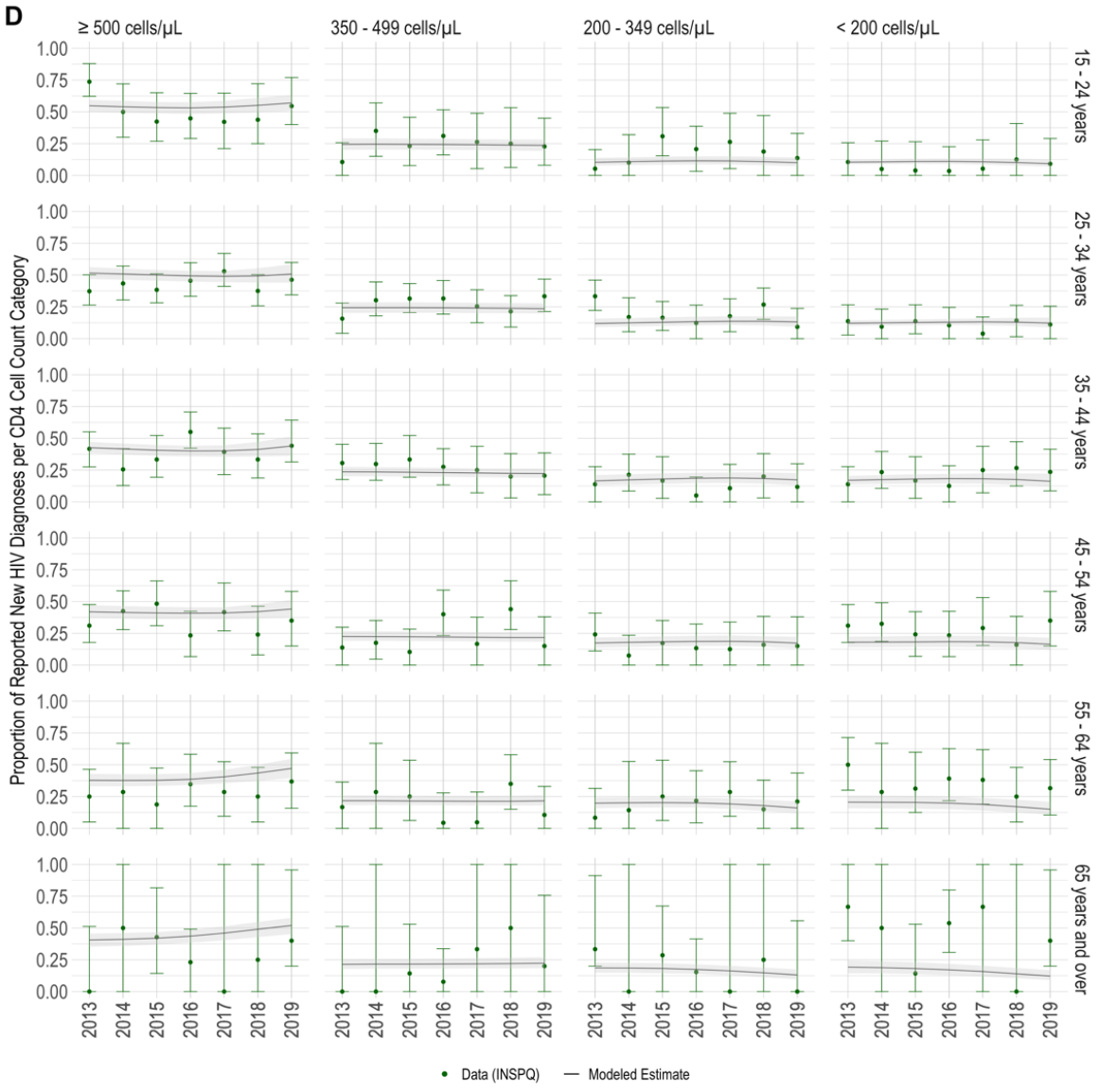


Figure 6.3.5. Model fits among men who have sex with men in the province of Québec

Model fits to the age-stratified calibration outcomes among men who have sex with men in the province of Québec: A) number of reported AIDS cases; B) number of reported new HIV diagnoses by age group; C) proportion of reported new HIV diagnoses that recently tested negative by age group; and D) proportion of reported new HIV diagnoses per CD4 cell count category and age group. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The coloured points and bars display the outcomes from the *Institut national de*

santé publique du Québec (INSPQ) data and their corresponding 95% confidence intervals, where applicable.

People who inject drugs

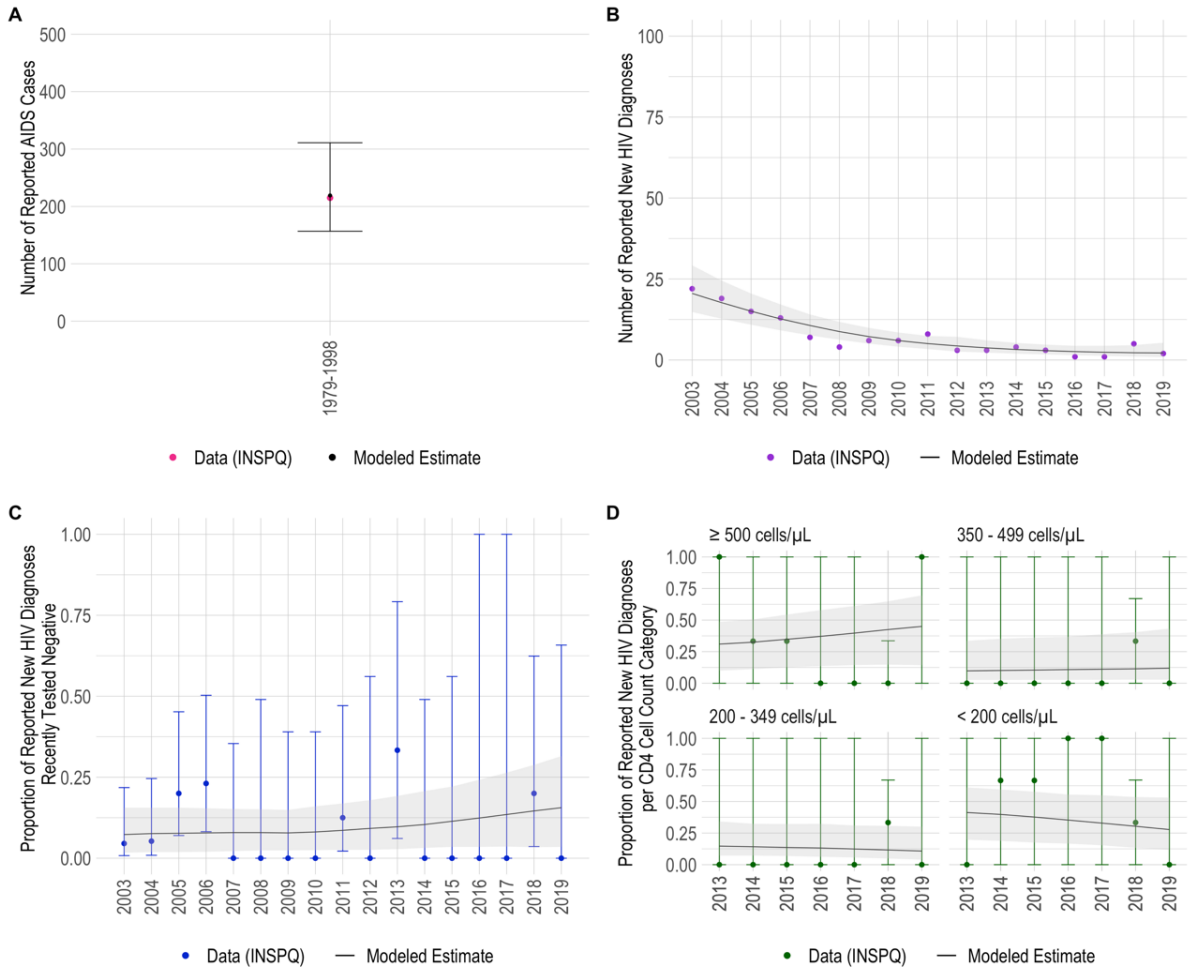


Figure 6.3.6. Model fits among males who injected drugs in Montréal
Model fits to the calibration outcomes among males who injected drugs in Montréal: A) number of reported AIDS cases; B) number of reported new HIV diagnoses; C) proportion of reported new HIV diagnoses that recently tested negative; and D) proportion of reported new HIV diagnoses per CD4 cell count category. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The coloured points and bars display the outcomes from the *Institut national de santé publique du Québec* (INSPQ) data and their corresponding 95% confidence intervals, where applicable.

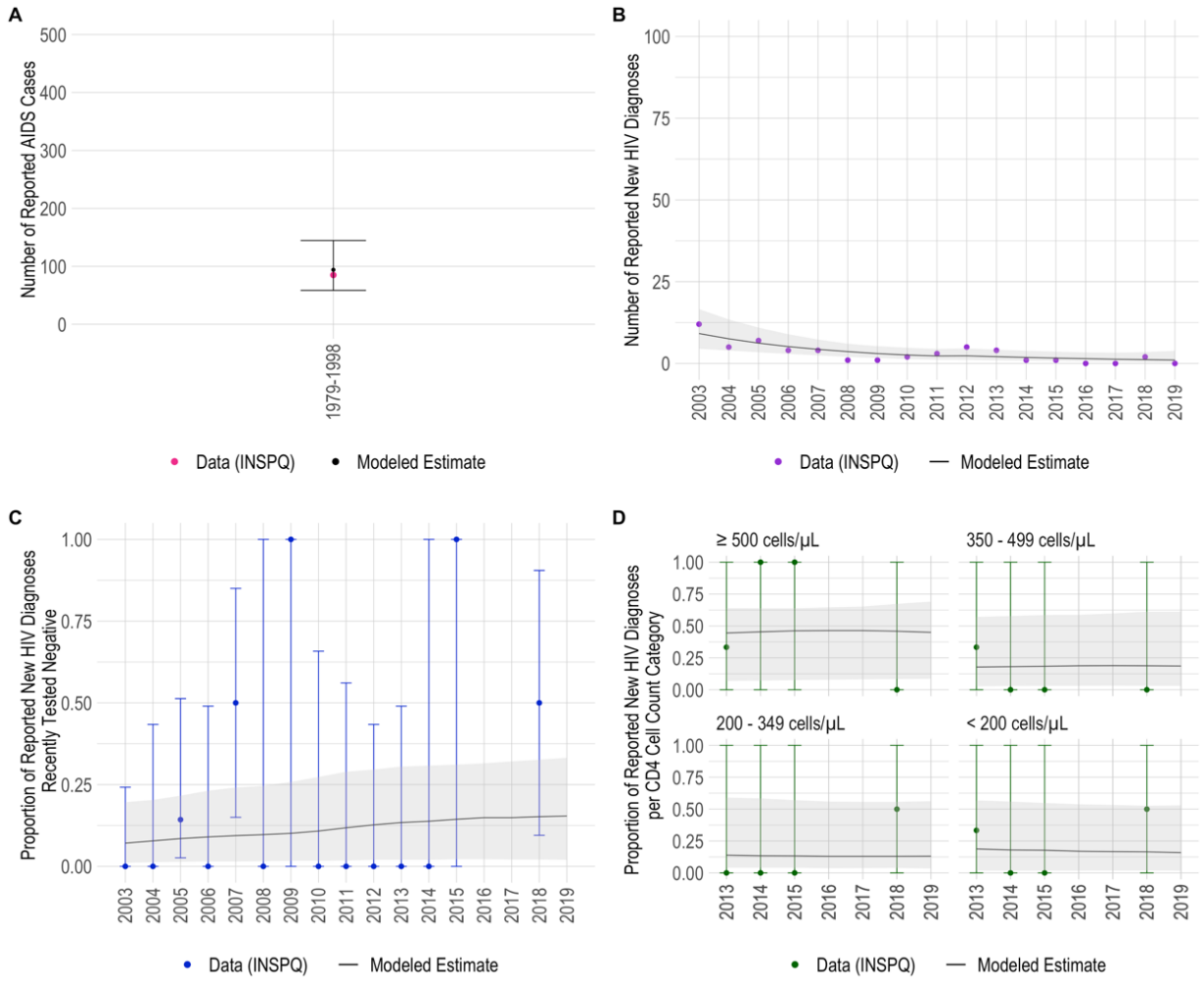


Figure 6.3.7. Model fits among females who injected drugs in Montréal

Model fits to the calibration outcomes among females who injected drugs in Montréal: A) number of reported AIDS cases; B) number of reported new HIV diagnoses; C) proportion of reported new HIV diagnoses that recently tested negative; and D) proportion of reported new HIV diagnoses per CD4 cell count category. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The coloured points and bars display the outcomes from the *Institut national de santé publique du Québec* (INSPQ) data and their corresponding 95% confidence intervals, where applicable.

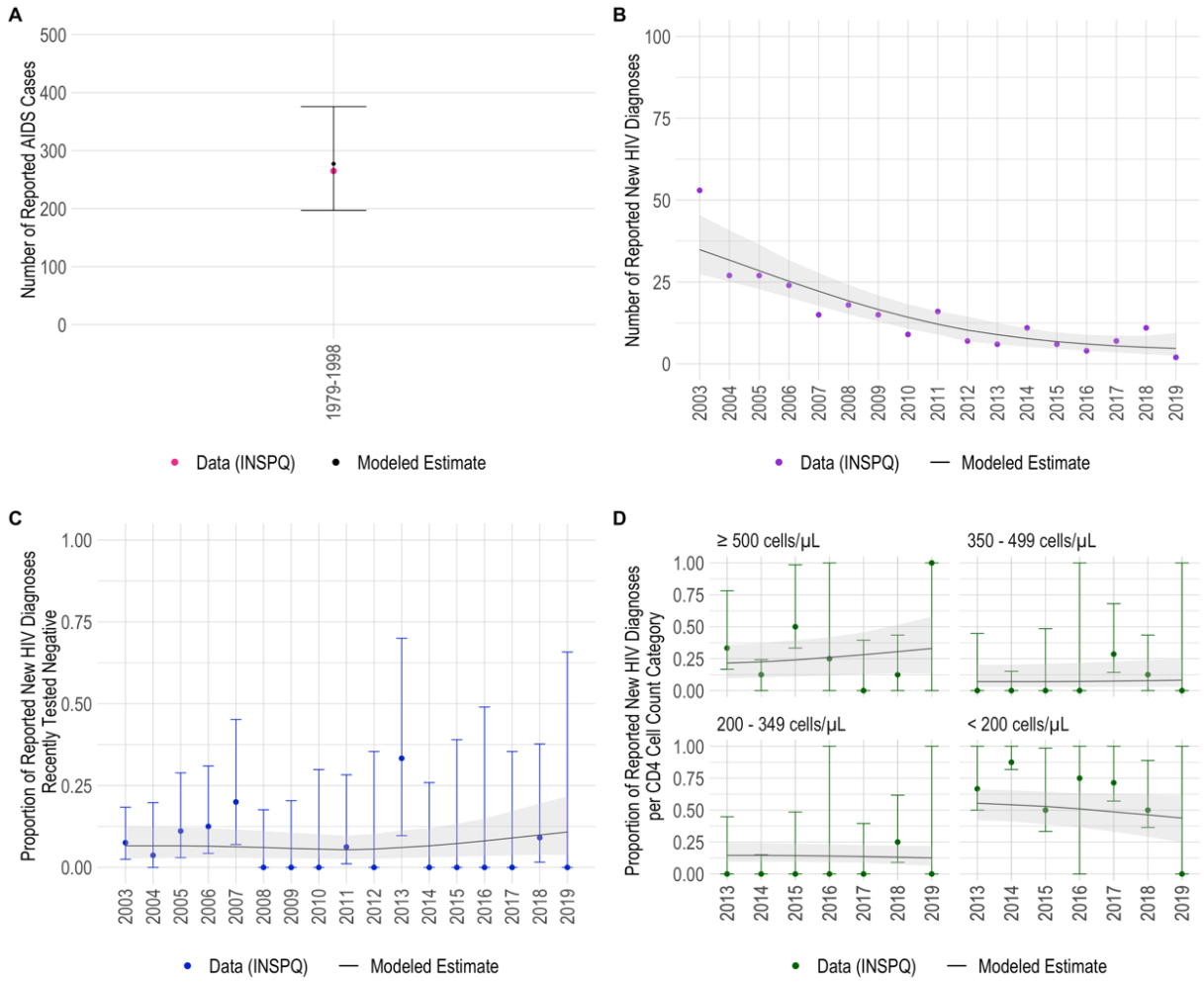


Figure 6.3.8. Model fits among males who injected drugs in the province of Québec
Model fits to the calibration outcomes among males who injected drugs in the province of Québec: A) number of reported AIDS cases; B) number of reported new HIV diagnoses; C) proportion of reported new HIV diagnoses that recently tested negative; and D) proportion of reported new HIV diagnoses per CD4 cell count category. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The coloured points and bars display the outcomes from the *Institut national de santé publique du Québec* (INSPQ) data and their corresponding 95% confidence intervals, where applicable.

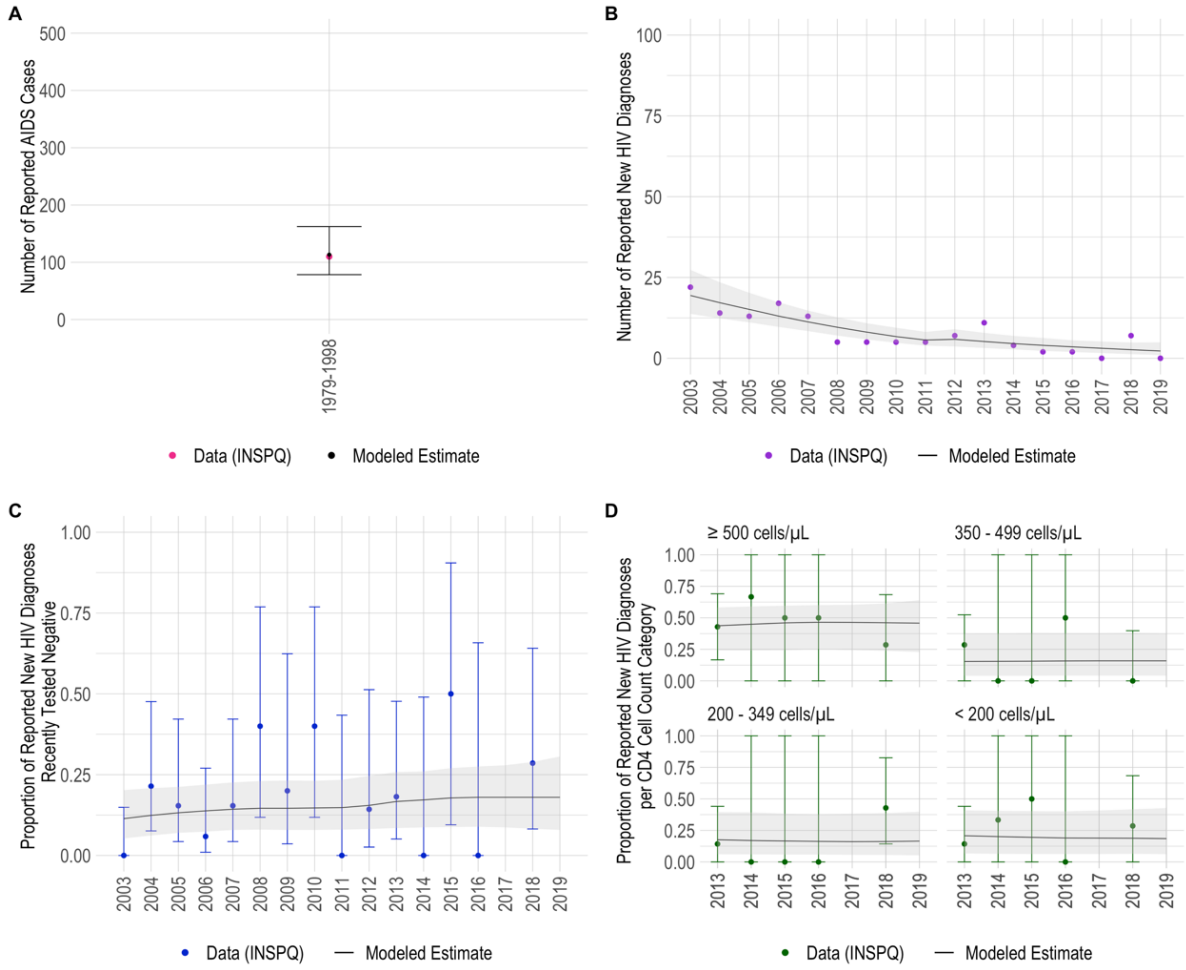


Figure 6.3.9. Model fits among females who injected drugs in the province of Québec

Model fits to the calibration outcomes among females who injected drugs in the province of Québec: A) number of reported AIDS cases; B) number of reported new HIV diagnoses; C) proportion of reported new HIV diagnoses that recently tested negative; and D) proportion of reported new HIV diagnoses per CD4 cell count category. The black points and lines display the model-predicted outcomes, with the black bars and grey bands showing their corresponding 95% credible intervals. The coloured points and bars display the outcomes from the *Institut national de santé publique du Québec* (INSPQ) data and their corresponding 95% confidence intervals, where applicable.

6.3.7. Appendix 7

Additional results: main analyses

Men who have sex with men

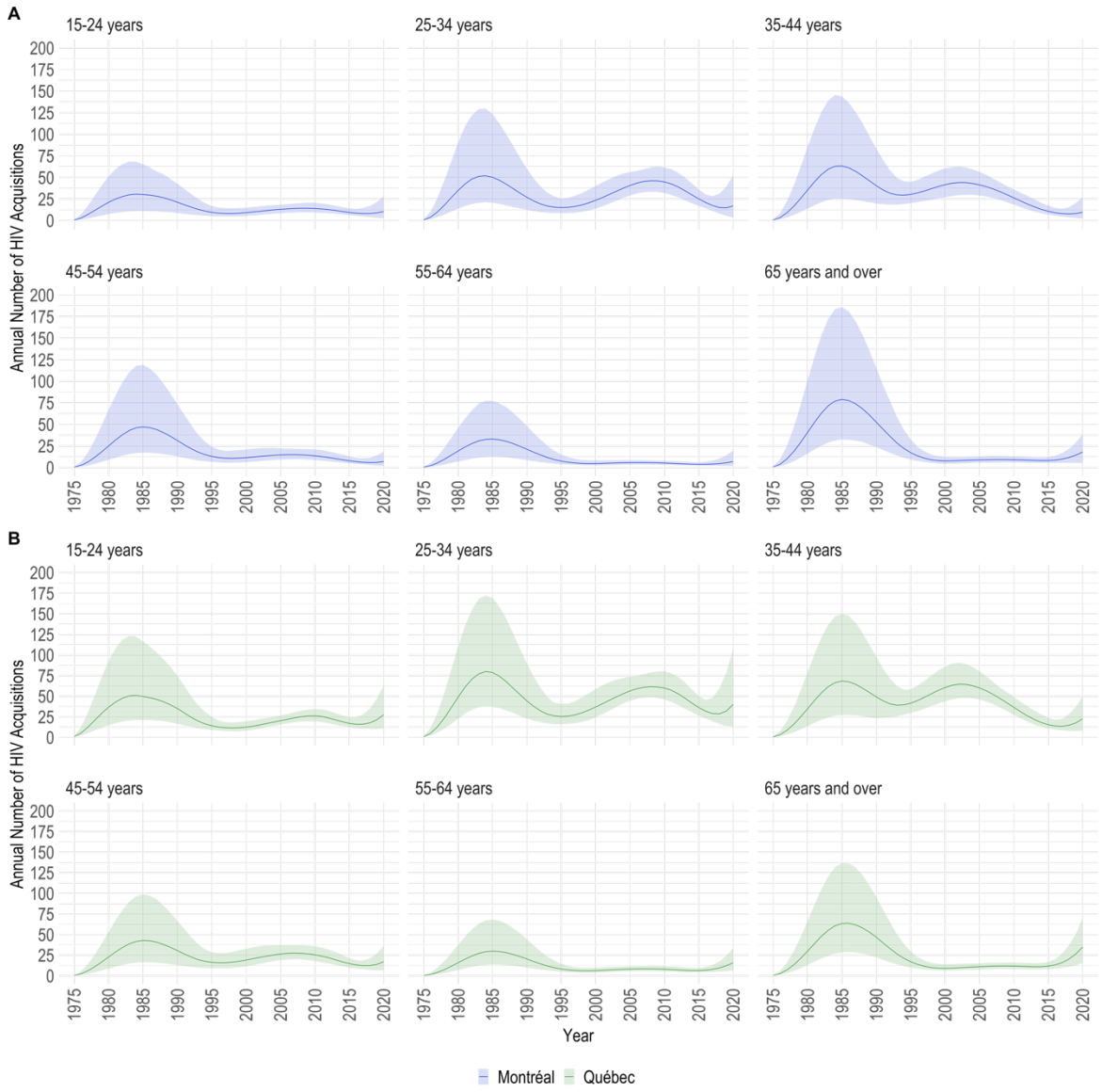


Figure 6.3.10. Estimated age-stratified incidence among men who have sex with men
Estimated age-stratified annual number of HIV acquisitions over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec, with incidence estimated per 10-year age group. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the

Montréal region (panel A) and green representing estimates for the whole province (panel B).

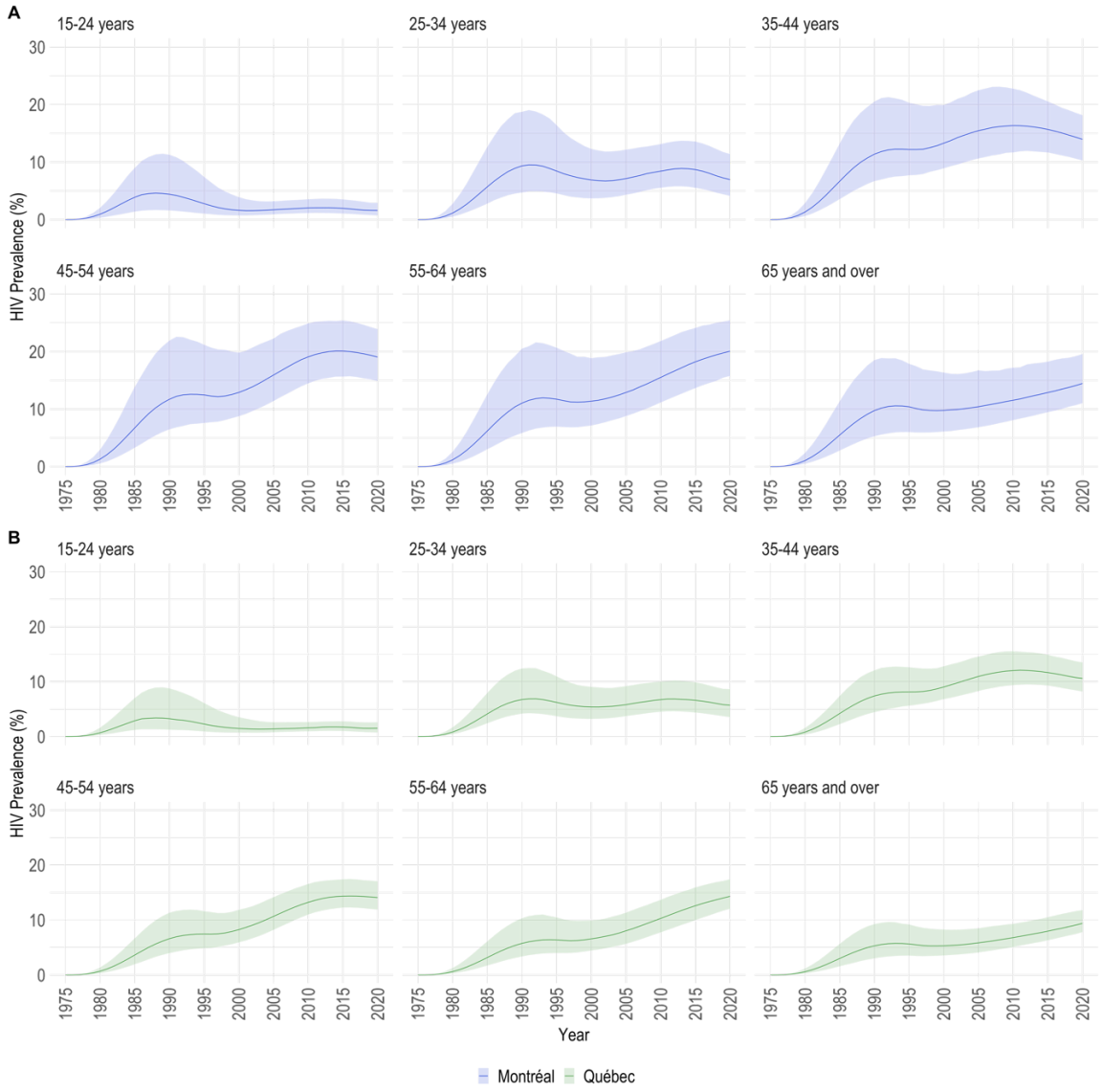


Figure 6.3.11. Estimated age-stratified prevalence among men who have sex with men

Estimated age-stratified HIV prevalence over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec, by 10-year age groups. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region (panel A) and green representing estimates for all of Québec (panel B).

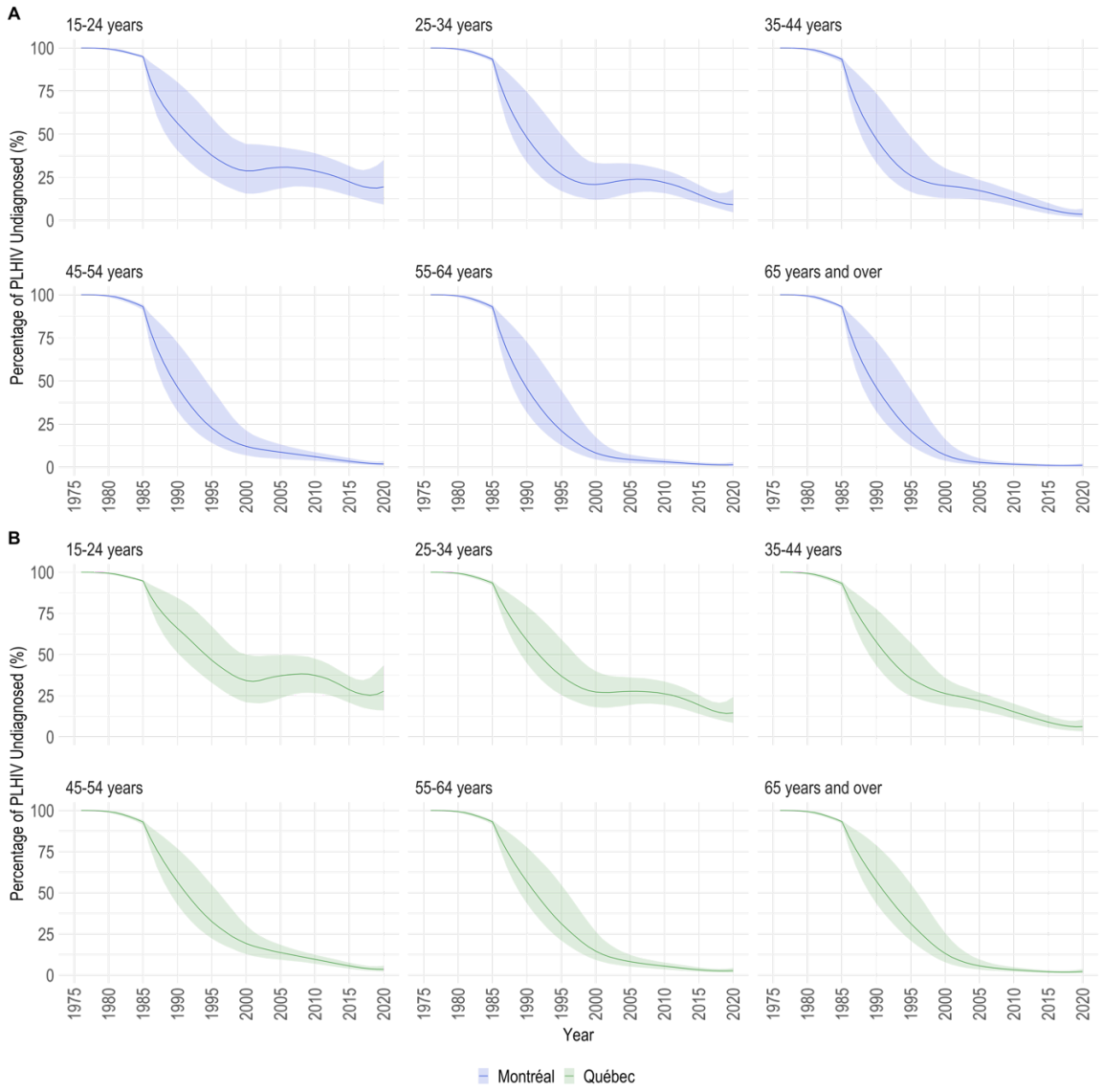


Figure 6.3.12. Estimated age-stratified percentage of PLHIV undiagnosed among men who have sex with men

Estimated age-stratified percentage of people living with HIV (PLHIV) undiagnosed over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec, by 10-year age groups. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region (panel A) and green representing estimates for all of Québec (panel B).

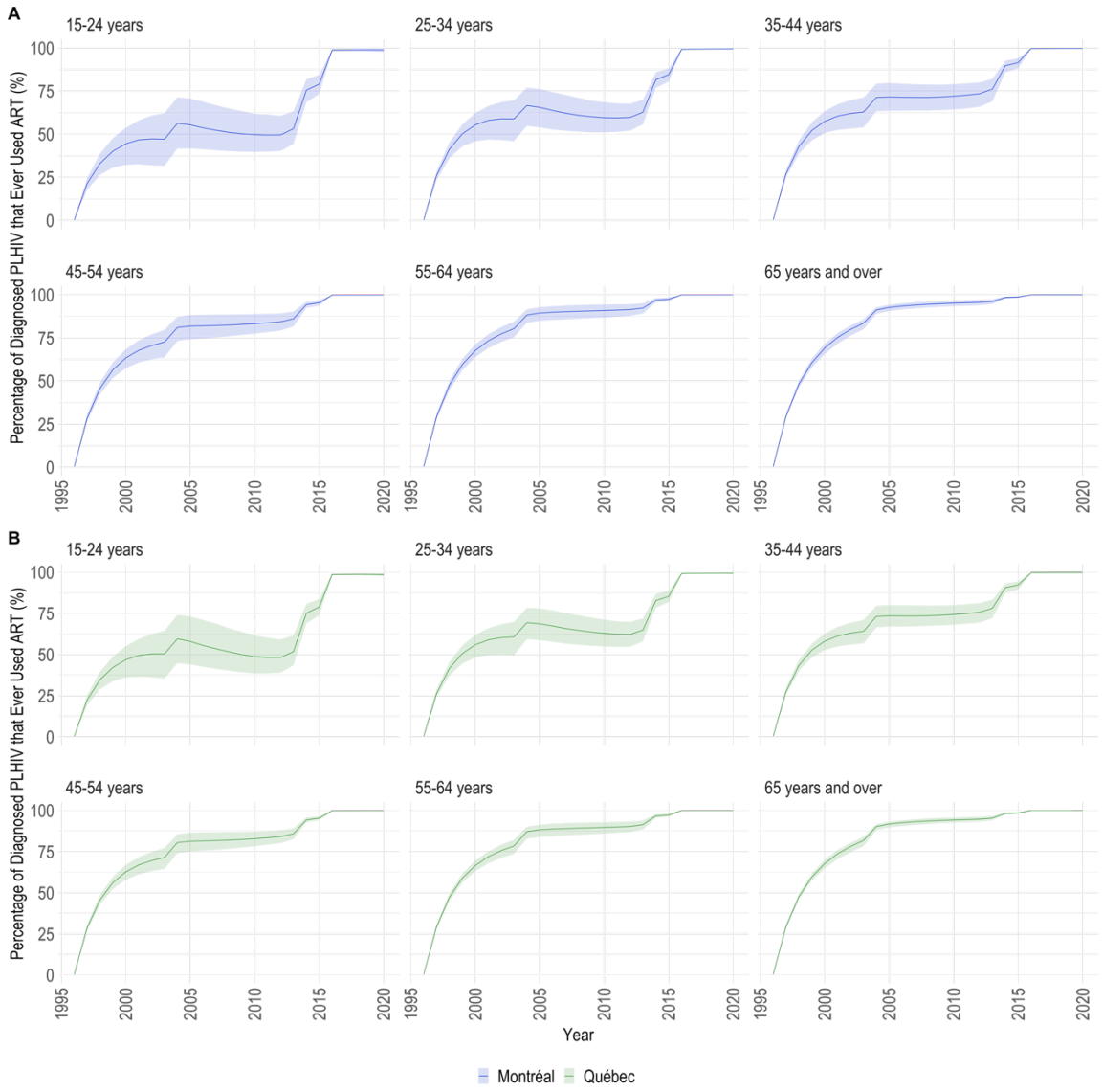


Figure 6.3.13. Estimated age-stratified percentage of diagnosed PLHIV that ever used ART among men who have sex with men

Estimated age-stratified percentage of diagnosed people living with HIV (PLHIV) that ever used antiretroviral treatment (ART) over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec, by 10-year age groups. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region (panel A) and green representing estimates for all of Québec (panel B).

People who inject drugs

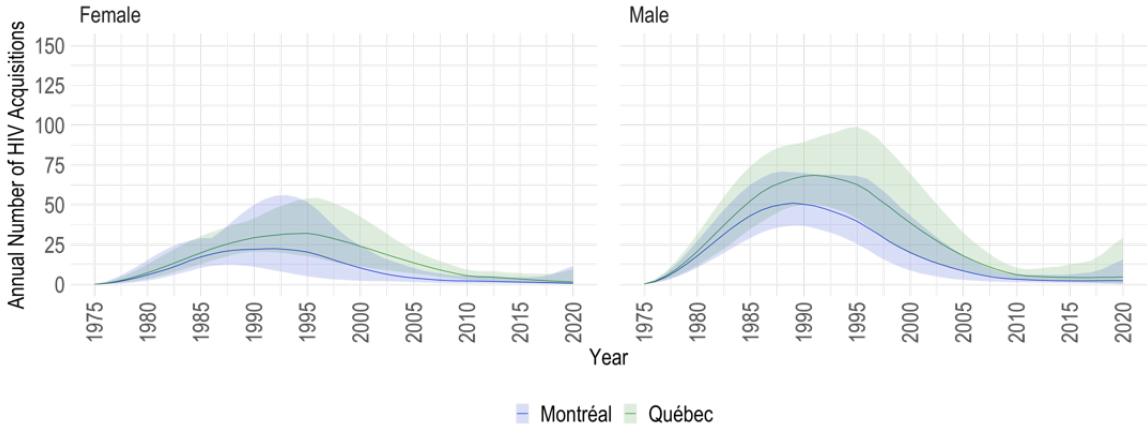


Figure 6.3.14. Estimated HIV incidence among active people who injected drugs by sex

Estimated annual number of HIV acquisitions over 1975-2020 among active females (panel A) and males (panel B) who injected drugs (PWID) in Montréal and the province of Québec. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for all of Québec.

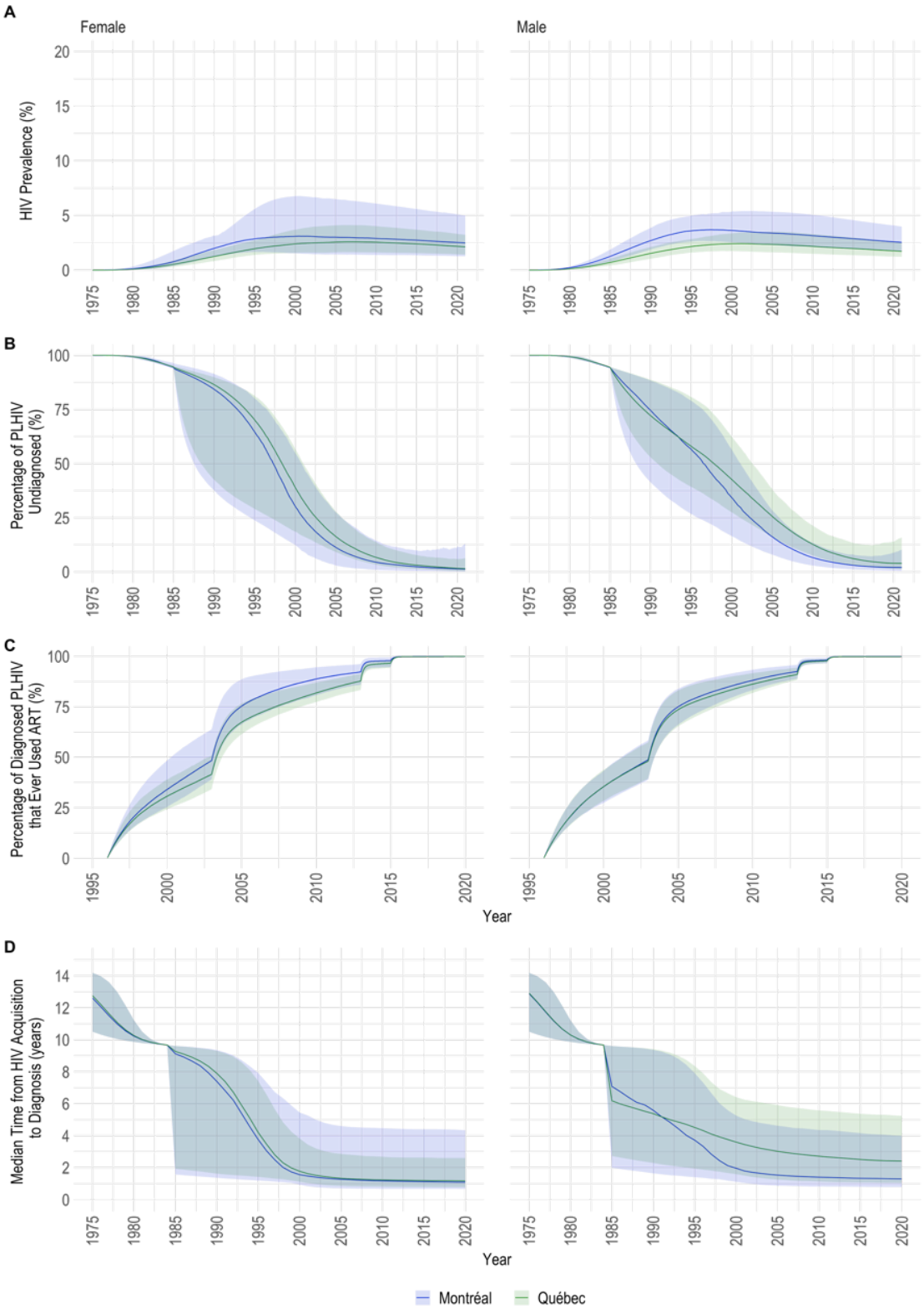


Figure 6.3.15. Estimated HIV prevalence, percentage of PLHIV undiagnosed, percentage of diagnosed PLHIV that ever used ART, and median time from HIv acquisition to diagnosis among active people who injected drugs by sex

Estimated HIV prevalence (panel A), percentage of people living with HIV (PLHIV) undiagnosed (Panel B), percentage of diagnosed PLHIV that ever used antiretroviral treatment (ART; panel C), and average time from HIV acquisition to diagnosis (panel D) over 1975-2020 among females and males who ever injected drugs (PWID) overall in Montréal and the province of Québec. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for all of Québec.

6.3.8. Appendix 8

Additional figures among MSM including available cross-validation comparison points

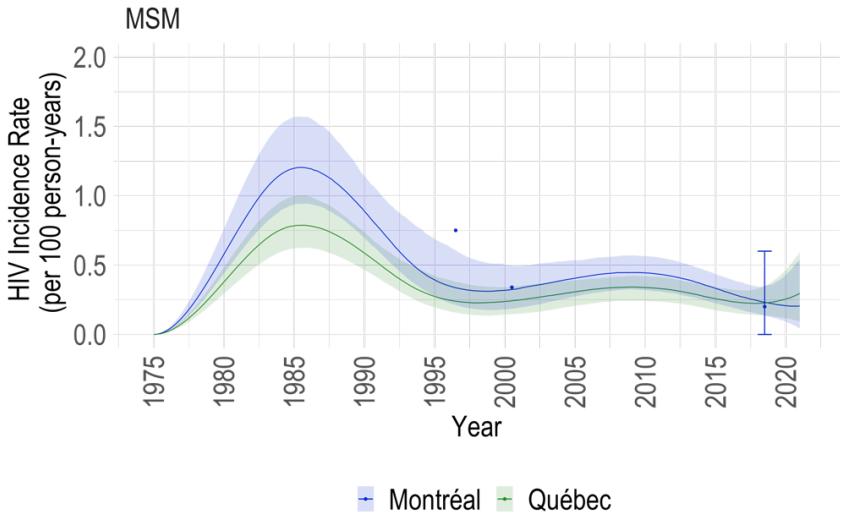


Figure 6.3.16. Estimated HIV incidence among men who have sex with men and available cross-validation data points

Estimated HIV incidence rate over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for the province of Québec. The points and bars display the Omega study[41] and Engage (Lambert G, personal communication, Dec. 2021) incidence rate estimates and corresponding 95% confidence intervals, respectively.

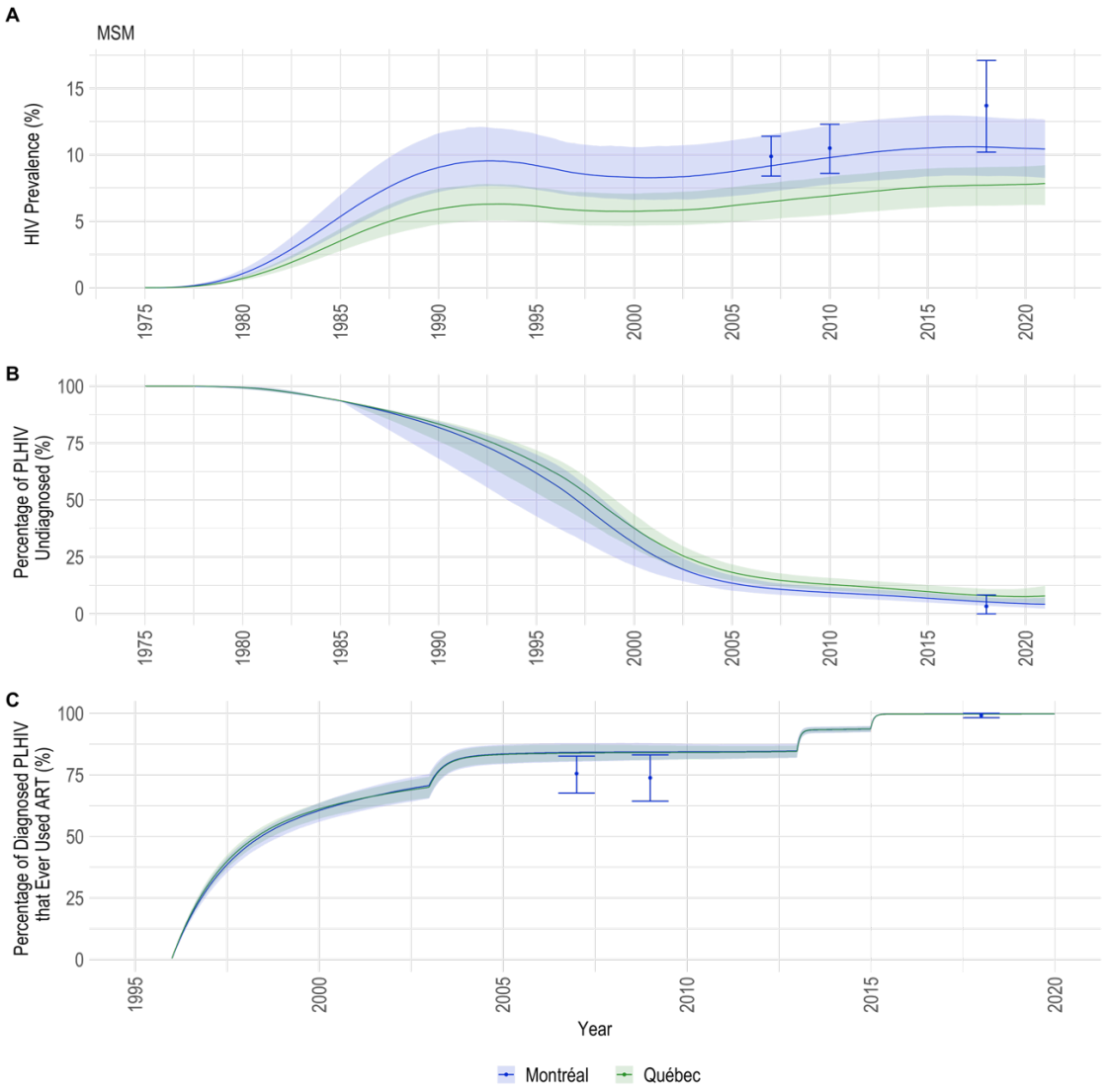


Figure 6.3.17. Estimated HIV prevalence, percentage of PLHIV undiagnosed, and percentage of diagnosed PLHIV that ever used ART among men who have sex with men and available cross-validation data points

Estimated HIV prevalence (panel A), percentage of people living with HIV (PLHIV) undiagnosed (panel B), and percentage of diagnosed PLHIV that ever used antiretroviral treatment (ART; panel C) including cross-validation data over 1975-2020 among men who have sex with men (MSM) in Montréal and the province of Québec. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for all of Québec. The points and bars in 2007 and 2010 display the estimates from Argus and their corresponding 95% confidence intervals, respectively. The points and bars from 2018 display the Engage estimates and corresponding 95% confidence intervals, respectively.

6.3.9. Appendix 9

AIDS-related mortality

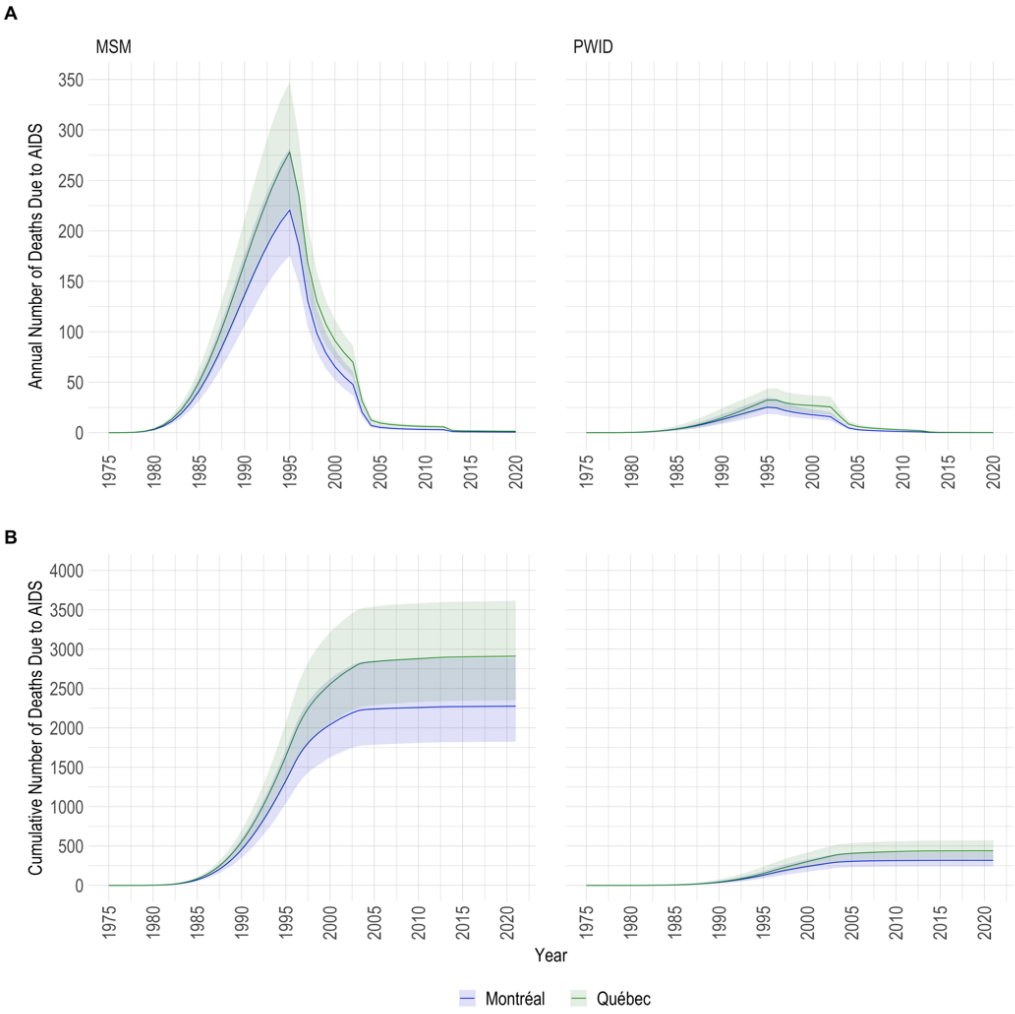


Figure 6.3.18. Estimated AIDS-related mortality
Estimated counts of AIDS-related mortality over 1975-2020 among men who have sex with men (MSM) and people who injected drugs (PWID) in Montréal and the province of Québec: A) the annual number of AIDS-related deaths; and B) the cumulative number of AIDS-related deaths. The coloured lines and bands display the posterior median and 95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for the province of Québec.

6.3.10. Appendix 10

Additional results: sensitivity analyses

Including 2020 data in model calibration

No reduction in testing rates over March 2020-year end

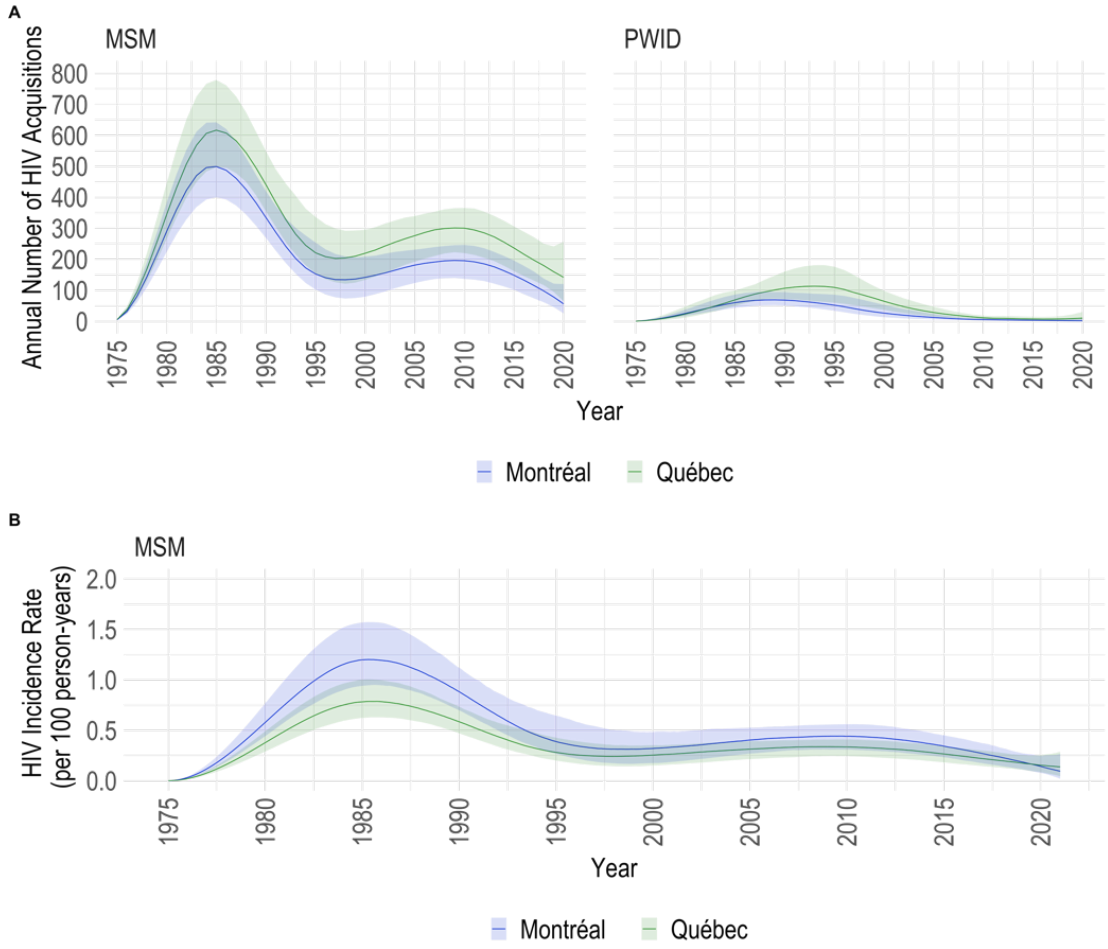


Figure 6.3.19. Estimated HIV incidence when 2020 data are included in model calibration and assuming no reduction in HIV testing rates

Estimated HIV incidence over 1975-2020 among men who have sex with men (MSM) and people who injected drugs (PWID) in Montréal and the province of Québec when 2020 data are excluded from model calibration and testing rates are not reduced during the COVID-19 pandemic: A) the annual number of HIV acquisitions among MSM and active PWID; and B) the HIV incidence rate among MSM. Incidence rates are not presented for PWID due to uncertainties in the denominator (the active PWID population size over time). The coloured lines and bands display the posterior median and 95% credible intervals,

respectively, with blue representing estimates from the Montréal region and green representing estimates for the province of Québec.

25% reduction in testing rates over March 2020-year-end

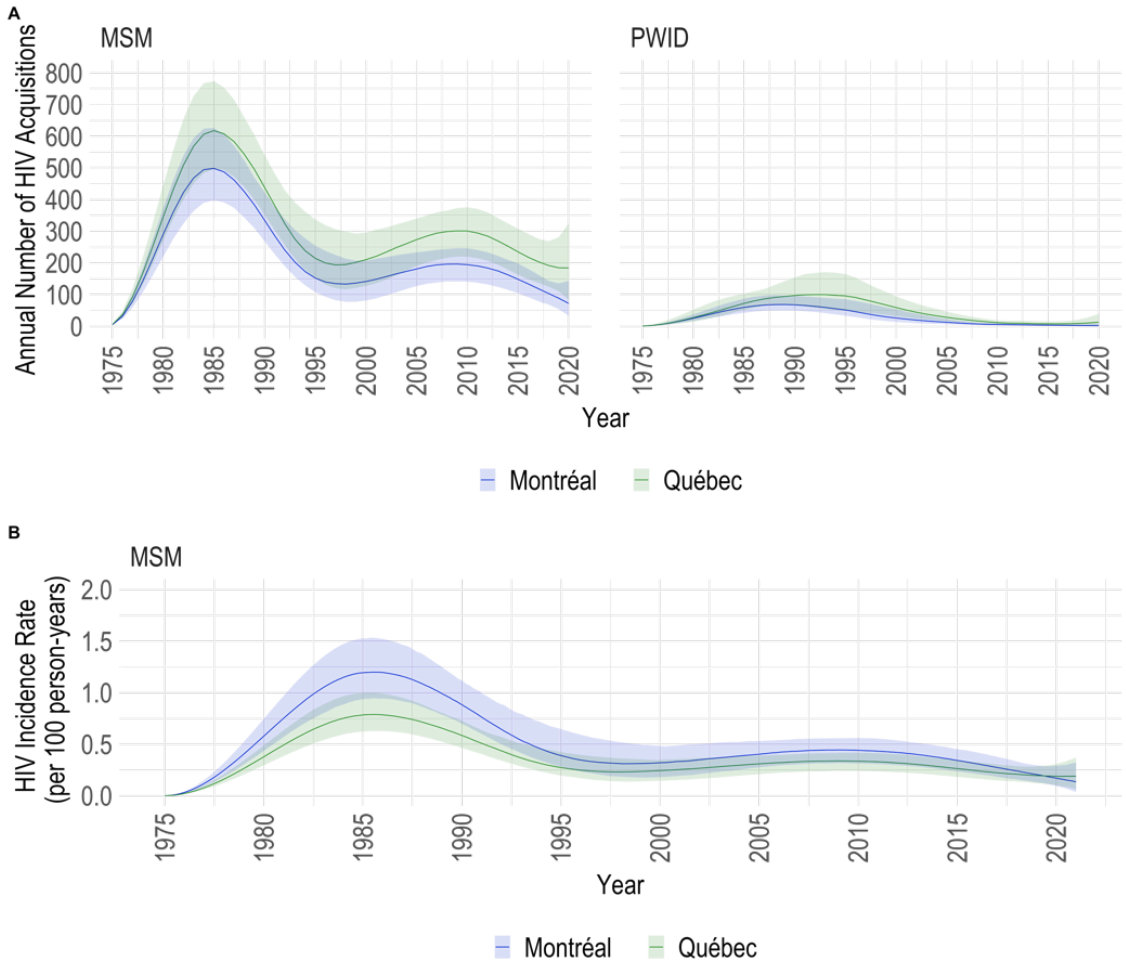


Figure 6.3.20. Estimated HIV incidence when 2020 data are included in model calibration and assuming a 25% reduction in HIV testing rates

Estimated HIV incidence over 1975-2020 among men who have sex with men (MSM) and people who injected drugs (PWID) in Montréal and the province of Québec when 2020 data are excluded from model calibration and testing rates are reduced by 25% during the COVID-19 pandemic (March 2020-year-end): A) the annual number of HIV acquisitions among MSM and active PWID; and B) the HIV incidence rate among MSM. Incidence rates are not presented for PWID due to uncertainties in the denominator (the active PWID population size over time). The coloured lines and bands display the posterior median and

95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for the province of Québec.

50% reduction in testing rates over March 2020-year-end

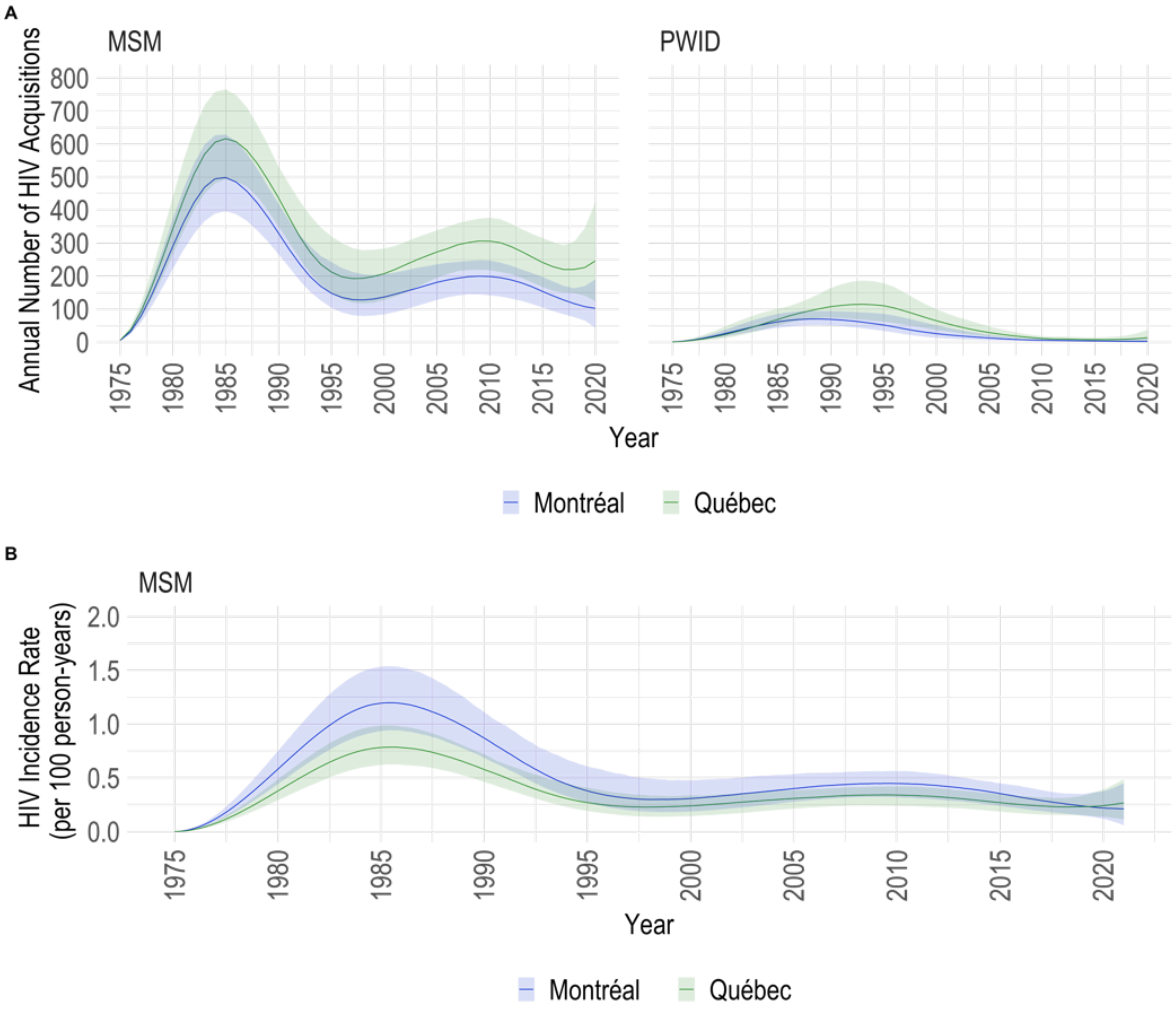


Figure 6.3.21. Estimated HIV incidence when 2020 data are included in model calibration and assuming a 50% reduction in HIV testing rates

Estimated HIV incidence over 1975-2020 among men who have sex with men (MSM) and people who injected drugs (PWID) in Montréal and the province of Québec when 2020 data are excluded from model calibration and testing rates are reduced by 50% during the COVID-19 pandemic (March 2020-year-end): A) the annual number of HIV acquisitions among MSM and active PWID; and B) the HIV incidence rate among MSM. Incidence rates are not presented for PWID due to uncertainties in the denominator (the active PWID population size over time). The coloured lines and bands display the posterior median and

95% credible intervals, respectively, with blue representing estimates from the Montréal region and green representing estimates for the province of Québec.

Table 6.3.14. Estimated HIV incidence, annual number of acquisitions, and percentage of people living with HIV undiagnosed in recent years (2017-2020) among men who have sex with men and people who inject drugs in Montréal and the province of Québec when 2020 data are included in model calibration and reductions in testing rates are explored[*]

Location	Year	% reduction in testing rates from March 2020–year end	Incidence rate (95%CrI) per 100 PY at year end[†]	Annual number of HIV acquisitions (95%CrI)	% PLHIV undiagnosed (95%CrI) at year end
Men who have sex with men					
Montréal	2017	0%	0.2 (0.1-0.3)	116 (74-161)	5.3 (3.6-7.4)
	2017	25%	0.2 (0.2-0.3)	118 (80-163)	5.4 (3.8-7.5)
	2017	50%	0.3 (0.2-0.4)	127 (84-170)	5.7 (4.1-7.8)
Montréal	2018	0%	0.2 (0.1-0.3)	98 (61-138)	4.7 (3.1-6.6)
	2018	25%	0.2 (0.1-0.3)	104 (68-143)	4.9 (3.4-6.8)
	2018	50%	0.2 (0.1-0.4)	116 (75-163)	5.2 (3.6-7.2)
Montréal	2019	0%	0.1 (0.1-0.2)	78 (46-121)	4.0 (2.6-5.9)
	2019	25%	0.2 (0.1-0.3)	89 (54-135)	4.3 (2.9-6.0)
	2019	50%	0.2 (0.1-0.4)	107 (65-170)	4.9 (3.2-6.9)
Montréal	2020	0%	0.1 (0.0-0.3)	56 (25-120)	3.4 (2.1-5.3)
	2020	25%	0.1 (0.0-0.3)	72 (32-143)	4.0 (2.6-6.1)
	2020	50%	0.2 (0.1-0.5)	102 (43-190)	5.2 (3.2-7.8)
Province of Québec	2017	0%	0.2 (0.1-0.3)	197 (131-271)	7.7 (5.5-10.0)
	2017	25%	0.2 (0.1-0.3)	204 (137-276)	7.9 (5.6-10.5)
	2017	50%	0.2 (0.2-0.3)	220 (150-294)	8.3 (6.1-10.8)
Province of Québec	2018	0%	0.2 (0.1-0.3)	180 (116-250)	7.0 (4.9-9.3)
	2018	25%	0.2 (0.1-0.3)	192 (125-269)	7.4 (5.2-10.0)
	2018	50%	0.2 (0.2-0.3)	220 (148-305)	7.9 (5.9-10.4)
Province of Québec	2019	0%	0.2 (0.1-0.3)	160 (95-242)	6.4 (4.5-8.7)
	2019	25%	0.2 (0.1-0.3)	185 (110-281)	6.9 (4.7-9.5)
	2019	50%	0.2 (0.1-0.4)	226 (141-346)	7.7 (5.6-10.4)
Province of Québec	2020	0%	0.1 (0.0-0.3)	142 (64-257)	5.9 (3.9-8.5)
	2020	25%	0.2 (0.1-0.4)	184 (84-325)	7.0 (4.5-10.1)
	2020	50%	0.3 (0.1-0.5)	246 (124-423)	8.6 (5.9-12.2)

Location	Year	% reduction in testing rates from March 2020–year end	Incidence rate (95%CrI) per 100 PY at year end[†]	Annual number of HIV acquisitions (95%CrI)	% PLHIV undiagnosed (95%CrI) at year end
People who inject drugs (includes active and past injectors)					
Montréal	2017	0%	-	2 (1-6)	2.1 (0.8-5.8)
	2017	25%	-	3 (1-6.5)	2.2 (0.8-5.9)
	2017	50%	-	2 (1-7)	2.2 (0.7-6.1)
Montréal	2018	0%	-	2 (1-6)	1.8 (0.7-5.4)
	2018	25%	-	2 (1-7)	1.9 (0.7-5.7)
	2018	50%	-	2 (1-7)	1.9 (0.6-6.2)
Montréal	2019	0%	-	2 (0-7)	1.6 (0.5-5.2)
	2019	25%	-	2 (0-7)	1.7 (0.6-5.4)
	2019	50%	-	2 (0-9)	1.7 (0.5-6.0)
Montréal	2020	0%	-	1 (0-9)	1.4 (0.4-5.1)
	2020	25%	-	2 (0-10)	1.6 (0.5-5.6)
	2020	50%	-	2 (0-10)	1.7 (0.4-6.8)
Province of Québec	2017	0%	-	7 (3-15)	3.3 (1.6-7.8)
	2017	25%	-	8 (4-17)	3.8 (1.9-9.1)
	2017	50%	-	8 (4-17)	3.4 (1.7-7.4)
Province of Québec	2018	0%	-	8 (3-17)	3.1 (1.5-7.5)
	2018	25%	-	9 (3-21)	3.7 (1.7-9.7)
	2018	50%	-	9 (4-20)	3.3 (1.6-7.7)
Province of Québec	2019	0%	-	9 (3-22)	3.1 (1.4-7.8)
	2019	25%	-	10 (3-28)	3.7 (1.6-10.3)
	2019	50%	-	11 (4-27)	3.3 (1.5-8.5)
Province of Québec	2020	0%	-	10 (3-30)	3.2 (1.3-8.3)
	2020	25%	-	13 (3-39)	4.0 (1.6-12.0)
	2020	50%	-	13 (4-36)	3.9 (1.6-10.2)

Abbreviations: Credible interval (CrI); person-years (PY); people living with HIV (PLHIV).

[*]Using the same incidence knot attributes shown above in Table 6.3.13.

[†]Only presented for men who have sex with men, due to uncertainties in the denominator for people who inject drugs (active injectors).

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Chapter 7. Conclusions and Implications

7.1. Summary of results

The UNAIDS targets and *Fast-Track City* goals are ambitious and elimination of HIV/AIDS epidemics poses new challenges for both surveillance and the public health response. Eliminating HIV as a public health threat will benefit some of the world's most vulnerable groups, for whom prevention needs have remained unmet for far too long. Even without a vaccine or a cure, we already have powerful tools to eliminate HIV. Guidance like the *HIV Prevention 2025 Road Map*[3] and initiatives like the *Fast-Track City* and *Political Declaration on HIV and AIDS*[5] are holding governments accountable and driving progress. My thesis aimed to support the ongoing elimination efforts in Montréal and Québec by describing the landscape of HIV prevention among gbMSM and informing the state of current epidemics among both gbMSM and PWID in the province.

In Manuscript 1, I described the HIV different prevention strategies reported by Montréal gbMSM in 2017-2018 and showed that, while condom use was highly prevalent, antiretroviral-based strategies emerged and gained importance. By 2018, it was clear that treatment-as-prevention and the "*undetectable = untransmissible*" messaging was having an effect among gbMSM living with HIV in Montréal, regardless of patterns in the use of other types of strategies. Among those whose HIV status was negative or unknown, PrEP use was central to the pattern of prevention practices (class) identified as biomedical prevention users. However, this class size was small (7% of HIV-negative gbMSM), reflecting potential barriers to access as this class encompassed gbMSM with higher education levels. Comparing participants engaged in the various identified prevention classes (where either condoms, seroadaptive behaviours, and biomedical strategies are central) to participants using fewer prevention strategies, I found that the prevention classes had more anal sex partners. In those whose HIV status was negative or unknown, the prevention classes were also more likely to have been recently diagnosed with an STBBI. This finding suggests that some gbMSM are evaluating their HIV acquisition risk, here proxied by an STBBI diagnosis, and are taking steps to mitigate it. This first manuscript improved our overall understanding of prevention use patterns, helped my team develop

and parameterize the mathematical models used in this thesis, and provided important context for my second manuscript.

In Manuscript 2, I used an agent-based model of sexual HIV transmission among gbMSM in Montréal to evaluate the population-level impact of PrEP use in Montréal over 2013-2021. Not surprisingly, the impact of PrEP depended on its coverage, which reached 10% among gbMSM whose HIV-status was negative at most. Barriers to access, uptake, retention, and/or re-initiation means that PrEP is not achieving its full potential. Increasing coverage by improving those barriers would have been the most efficient way for the intervention to have prevented more HIV acquisitions during the study period. From 2015-2021, PrEP cumulatively prevented 20% (90%CrI: 11%-30%) of HIV acquisitions. If PrEP coverage in Montréal had instead followed the one observed in Vancouver, 63% (90%CrI: 54%-70%) of the estimated HIV acquisitions would have been averted. With PrEP provided free in British Columbia, the differential uptake between the Montréal and Vancouver has been attributed to financials barriers[141]. This represents a missed opportunity that would have brought Montréal considerably closer to its target of zero acquisitions at a time when incidence was higher.

To further benchmark elimination efforts, in Manuscript 3, I created a mathematical model synthesizing surveillance data to estimate HIV incidence and important epidemic indicators (e.g., 95-95-95, efficiency of HIV testing services) in Québec for two important key populations: gbMSM and PWID. The results from this model showed important incidence declines in these populations over the last three decades. As we inch closer to elimination, however, the rates of declines have slowed. Further, Montréal did not meet its *Fast-Track City* goal of zero acquisitions by 2020. That year, there were an estimated 266 (95%CrI: 103-508) gbMSM and 6 (95%CrI:1-26) PWID acquisitions in Québec, of which 97 (95%CrI: 33-227) and 2 (95%CrI: 0-14), respectively, were acquired in Montréal. The incidence reductions among PWID are notable and suggest that NSP, OAT, treatment-as-prevention, and the recent supervised injection sites are reducing acquisition risk in this historically vulnerable group. Moreover, the city and the province are on track towards the 95-95-95 goals, having already achieved <10% undiagnosed and high ART coverage in 2020 among both gbMSM and PWID. Diagnosis of HIV in Montréal does not seem to be

a bottleneck anymore, with the time from acquisition-to-diagnosis estimated to be <2 years in 2020. In addition to setting benchmarks, my work suggested some opportunities for Montréal and Québec to close in on the first 95 (PLHIV aware of their status) by lessening the slight regional disparities identified in the undiagnosed fraction of PLHIV outside of the Montreal public health unit and in younger gbMSM.

7.2. Strengths and limitations

My thesis results should be interpreted considering several limitations, in addition to those outlined in the respective manuscripts, ranging from data issues to modeling challenges. First, HIV is not legally notifiable on a regional basis in Québec. This decision was taken largely due to the preference of community members, who feared the potential consequences of being identified, including stigmatization, and the repercussions of using HIV testing services. The advantage of such a policy is that it can encourage testing for those who may not otherwise access such services. For research purposes, however, this does pose a few practical limitations, including the inability of quantifying the treatment and care cascade using surveillance data. For instance, provincial authorities are unable to link PLHIV to provincial health care and prescription data, making it challenging to characterize the cascade in real-time. In addition, if individuals have been diagnosed at anonymous sites (e.g., community-based settings) and re-test elsewhere, they might be counted as a "new diagnosis" even though they have already been diagnosed. Similarly, individuals previously diagnosed migrating into the province are considered "old diagnosis", however, information on migration patterns is often not available and the most likely region of acquisition is unknown.

Practical limitations regarding the COVID-19 pandemic arose for each manuscript in this thesis. Firstly, the interpretation of the findings in Manuscript 1 could be affected. That article included data before 2020 and it is plausible that prevention practice patterns have changed following COVID-19 disruptions and lock-downs, which affected both prevention uptake and sexual behaviors. To address these issues in the other manuscripts, I either simulated hypothetical scenarios assuming that PrEP did not change over the COVID-19

pandemic (Manuscript 2) or restricted our estimates of incidence to 2020 (Manuscript 3) while further surveillance data is collected.

Strengths of this thesis include some data, methodological, and conceptual advantages. For instance, I adopted an analysis framework that is status-neutral and that considers the prevention needs of people living with and without HIV, as highlighted in Chapter 2 and Manuscript 1. In terms of methods, the mathematical model considered treatment-as-prevention and use of other prevention strategies among PLHIV in Manuscript 2. In Manuscript 3, my model captured HIV diagnosis and treatment, and was therefore able to investigate the unmet diagnostic needs of gbMSM and PWID living with HIV, as well as the treatment and care continuum.

Finally, in terms of data, I had access to the *Engage Cohort* for all my manuscripts. *Engage* is the first study of gbMSM in Montréal that used RDS as a recruitment strategy, making it the most representative sample to date. The previous study of combination HIV prevention use by gbMSM in Montréal recruited participants from a clinical setting, making it a convenience sample of gbMSM accessing STBBI care. Moreover, estimates of the third 90 (the percentage of diagnosed PLHIV with a suppressed viral load) for Montréal gbMSM have previously come from clinical cohort data[142, 143]. In Manuscript 2, longitudinal analysis of the *Engage* PrEP data elevated the level of detail with which I could inform the model's PrEP module in terms of current and lifetime use. Finally, in Manuscript 3, I could parameterize HIV testing and treatment parameters with *Engage* data, as well as cross-validate the model-estimated incidence with those from the *Engage Cohort*. Given the infrequent occurrence of HIV acquisition in the cohort, modeled estimates can increase the precision and granularity of HIV incidence estimates.

Leveraging detailed surveillance data in collaboration with epidemiologists from the INSPQ was also a significant strength of my thesis. I had access to 18 years of this epidemiological data, making it an exceptional source for building the mathematical models used in Manuscripts 2 and 3. In addition to knowing new diagnoses per year, the data contained two measures of recency, i.e., CD4 cell counts at diagnoses and the self-

reported time since last HIV negative test. These measures especially enhanced the ability to discern HIV incidence in the models.

7.3. Implications

The *HIV Prevention 2025 Road Map* recommend examining HIV programme needs and barriers[3]. It adopts an HIV precision prevention approach to achieve programmatic goals[3]. Overall, my thesis objectives are aligned with these recommendations and my findings come together as a basis to examine HIV epidemics in Montréal and Québec and guide programs as they continue to evolve to eliminate HIV as a public health threat.

I identified prevention strategies and indicated that PrEP use could be scaled up and more widely promoted (Manuscript 1). HIV prevention campaigns must reach a large audience that includes vulnerable priority groups to enhance their effectiveness. In my evaluation of PrEP's population level impact (Manuscript 2), I showed that its effect could have been substantially higher in Montréal if coverage was greater. Cost free options could improve access to PrEP, as seen in British Columbia. In the future, injectable long-acting PrEP may be approved in Canada and, in a context of low incidence, stakeholders should consider its use by individuals who have adherence or retention issues with oral PrEP. Fully investigating all missed opportunities and advancing the understating of barriers to PrEP and other new interventions could help achieve HIV elimination.

In this thesis, I also built a tool for epidemiological intelligence that could potentially be used for routine monitoring and assessment of HIV elimination targets. The level of granularity provided enables the monitoring of epidemic trends among gbMSM and PWID by sex and age, aiding public health in recognizing populations in need of targeted HIV testing and prevention services.

7.4. Conclusions

In Québec, important strides have been made to address the HIV epidemic, however, elimination of HIV as a public health threat hinges on reaching zero new HIV acquisitions. In my work, I identified areas where improvements can be made to reach the HIV

elimination targets in Québec. Increasing PrEP coverage by expanding awareness and access to all who could benefit from its use would enhance the intervention's population-level effectiveness. To this end, identifying disparities and barriers to PrEP access, retention, and re-initiation –and addressing those– will be key. In addition, prioritizing HIV testing for younger gbMSM and ensuring adequate access to such services outside urban centers will help close these gaps. Lastly, as HIV epidemic drivers and the prevention landscape continue to evolve, close monitoring of trends and the impact of interventions among key populations using some of the tools developed in this doctoral thesis are necessary.

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