Chemsex, sexually transmitted infections, and pre-exposure prophylaxis among men who have sex with men: longitudinal analyses of sexual health clinic attendees in Montréal

Jorge Luis Flores Anato
Department of Epidemiology, Biostatistics and Occupational Health
McGill University, Montréal

July 2021

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Epidemiology

Abstract

Background: Chemsex –the use of illicit substances during sex to enhance pleasure– has become more prevalent in the last decade among gay, bisexual and other men who have sex with men (gbMSM). This has raised public health concerns because chemsex can be associated with transmission of HIV and other sexually transmitted infections (STIs). Pre-exposure prophylaxis (PrEP) is highly effective at preventing HIV and is recommended for gbMSM and transgender women at elevated risk of HIV acquisition. As PrEP can provide an important prevention tool for people who practice chemsex, it is important to better understand the role of chemsex in PrEP use and STI incidence.

Objectives: Understand the evolving patterns of chemsex practices among gbMSM and transgender women consulting for PrEP in Montréal (Canada) and their impact on STI transmission among PrEP users by:

(1) describing temporal trends in chemsex practices and their impact on PrEP trajectories, and

(2) estimating the impact of chemsex on incidence of gonorrhea and chlamydia among PrEP users.

Methods: The l'*Actuel PrEP Cohort* was established in 2013 at the *Clinique médicale l'Actuel*, a major sexual health clinic in Montréal. For the purposes of this thesis, the cohort was restricted to adult (≥18 years-old) gbMSM and transgender women who consulted for PrEP between 2013–2020. This dataset includes baseline sociodemographic and behavioural data, and quarterly follow-up behavioural and STI screening data. I first described the sociodemographic profile of clients who consulted for PrEP, characterized chemsex and polysubstance use trends over time, and evaluated PrEP trajectories. Then, for the second objective, I used survival analyses to estimate the effect of chemsex at baseline on incidence of gonorrhea and chlamydia, focusing on the 24 months following PrEP initiation. I also investigated the role of polysubstance use and potential effect modification by age, education, and income.

Results: A total of 2,923 clients consulted for PrEP between 2013–2020 (2,910 cisgender gbMSM, 6 transgender gbMSM, 7 transgender women). Among these clients, 24% reported any chemsex and 13% reported polysubstance use in the past year. Ecstasy (14%), GHB (13%),

and cocaine (12%) were the most commonly reported chemsex substances. Prevalence of chemsex and polysubstance use decreased over time. The proportion of clients initiating PrEP (73%) was similar between groups, and the median time to discontinuation was also similar: 6.5 months (95% CI: 5.3–7.2) in the chemsex group compared to 6.9 months (95% CI: 6.3–7.5) in the no-chemsex group.

There were 2,086 clients (2,079 cisgender gbMSM, 3 transgender gbMSM, 4 transgender women) who initiated PrEP, contributing 1,477 person-years of follow-up. There was no incident HIV infection among clients on PrEP. When controlling for age, education, income, PrEP regimen, and year of baseline consultation, chemsex was linked to a 32% higher hazard of gonorrhea or chlamydia diagnosis (adjusted HR=1.32; 95% CI: 1.10–1.57). This effect was stronger among clients reporting polysubstance use (adjusted HR=1.51; 95% CI: 1.21–1.89). The strength of the effect of chemsex on STI incidence varied by age, education, and income.

Conclusions: One in four gbMSM consulting for PrEP at a large Canadian sexual health clinic reported chemsex in the past year. Chemsex, however, is not an obstacle to PrEP initiation or persistence. Among PrEP users, chemsex at baseline is linked to increased incidence of gonorrhea and chlamydia. Incidence was higher for people who report two or more chemsex substances. The high prevalence of chemsex practices and high STI incidence highlight the need for integrated services addressing unmet needs at the intersection of sexual health and substance use. The high STI incidence also stresses the importance of PrEP as an effective HIV prevention tool for this population.

Résumé

Contexte : L'utilisation de drogues illicites au cours d'actes sexuels (le chemsex) est devenue plus fréquente durant la dernière décennie chez les hommes gais, bisexuels et autres hommes ayant des relations sexuelles avec d'autres hommes (gbHARSAH). Cela inquiète les experts en santé publique car le chemsex pourrait être associé à un plus grand risque de transmission du VIH et d'autres infections transmissibles sexuellement (ITS). La prophylaxie préexposition (PrEP) est très efficace pour prévenir la transmission du VIH et est recommandée pour les gbHARSAH et femmes transgenres à risque élevé de contracter le VIH. La PrEP représente une méthode de prévention importante pour ceux qui pratiquent le chemsex, mais l'impact de cette pratique sur l'utilisation de la PrEP et l'incidence des ITS doit être mieux documenté.

Objectifs : Améliorer notre compréhension des pratiques de chemsex chez les gbHARSAH et femmes transgenres consultant pour la PrEP à Montréal (Canada) et leur impact sur la transmission d'ITS chez les utilisateurs de la PrEP. Spécifiquement, les deux objectifs suivants seront poursuivis :

(1) décrire les tendances de chemsex à travers le temps et l'impact de cette pratique sur les trajectoires PrEP, et

(2) estimer l'impact du chemsex sur l'incidence de gonorrhée et chlamydia parmi les utilisateurs de la PrEP.

Méthodes : La Clinique médicale l'Actuel –une importante clinique de santé sexuelle à Montréal– a établi en 2013 la cohorte PrEP de l'Actuel. Pour ce mémoire, les gbHARSAH et femmes transgenres de plus de ≥18 ans qui ont consulté pour la PrEP entre 2013–2020 ont été retenus. Les données démographiques et comportementales collectées à la 1ère visite, ainsi que les données comportementales et sur le dépistage d'ITS pendant le suivi trimestriel, ont été utilisées. Pour le 1er objectif, j'ai décrit le profil sociodémographique des clients consultant pour la PrEP, leurs tendances de chemsex et de polyconsommation à travers le temps, et leurs trajectoires PrEP. Pour le 2ème objectif, j'ai utilisé des analyses de survie pour estimer l'effet du chemsex rapporté au départ sur l'incidence de gonorrhée et chlamydia pendant les 24 mois suivant l'initiation PrEP. J'ai aussi examiné le rôle de la polyconsommation et des modificateurs d'effet potentiels tels l'âge, l'éducation, et le revenu.

Résultats : Entre 2013–2020, 2 923 clients ont consulté pour la PrEP (2 910 gbHARSAH cisgenres, 6 gbHARSAH transgenres, 7 femmes transgenres). La prévalence du chemsex était de 24% et celle de la polyconsommation de 13%. Les drogues le plus populaires étaient l'ecstasy (14%), le GHB (13%) et la cocaïne (12%). La prévalence du chemsex et de la polyconsommation a diminué avec le temps. Le taux d'initiation (73%) de la PrEP était similaire entre les deux groupes et le temps médian avant l'arrêt de la PrEP aussi : 6.5 mois (IC à 95%: 5.3–7.2) (groupe chemsex) comparé à 6.9 mois (IC à 95%: 6.3–7.5) (groupe qui n'a pas rapporté du chemsex).

Il y a eu 2 086 clients (2 079 gbHARSAH cisgenres, 3 gbHARSAH transgenres, 4 femmes transgenres) qui ont initié la PrEP et contribué au total 1 477 années-personne de suivi. Il n'y a eu aucun diagnostic incident du VIH. En ajustant pour l'âge, l'éducation, le revenu, le régime PrEP, et l'année de visite initiale, le risque d'un diagnostic incident de gonorrhée ou chlamydia était 32% plus haut parmi les clients qui ont rapporté du chemsex (rapport de risque ajusté=1,32; IC à 95%: 1,10–1,57). Cet effet était plus fort parmi ceux rapportant de la polyconsommation (rapport de risque ajusté=1,51; IC à 95%: 1,21–1,89). L'effet du chemsex était modifié par l'âge, l'éducation, et le revenu.

Conclusions : Parmi les gbHARSAH consultant pour la PrEP, un client sur quatre rapporte du chemsex dans la dernière année. Cependant, cette pratique n'est pas un obstacle à l'initiation ou la persistance sur la PrEP. Chez les utilisateurs de la PrEP, le chemsex est lié à une plus forte incidence de gonorrhée et chlamydia. Cet effet est encore plus grand pour ceux rapportant de la polyconsommation. La prévalence élevée de chemsex et l'incidence élevée d'ITS mettent en évidence des besoins non comblés pour des services intégrés à l'intersection de la santé sexuelle et la consommation de drogues. L'incidence élevée des ITS démontre aussi l'importance de la PrEP en tant que méthode de prévention du VIH pour cette population.

Preface

This thesis focuses on the chemsex practices, the pre-exposure prophylaxis (PrEP) trajectories and the impact of chemsex on the incidence of sexually transmitted infections (STIs) in a cohort of PrEP users composed predominantly of gay, bisexual and other men who have sex with men (gbMSM). The thesis is organized as follows. In the introduction, I start by situating this research –in particular the topics of chemsex and PrEP– within the wider context of the HIV/AIDS epidemic in Québec. In Chapter 1, I review the evidence base related to the practice of chemsex among gbMSM, the rising incidence of STIs among gbMSM, and the role of PrEP as a biomedical intervention for HIV prevention. Chapter 2 presents the objectives of this work. Chapter 3 provides a description of the study population and the methodology used. Chapters 4 and 5 describe the analyses and results in the form of two manuscripts. I discuss the significance of these results within the wider literature on chemsex, PrEP, and STIs in Chapter 6 and provide concluding remarks in Chapter 7.

This thesis has been prepared according to the guidelines for a *Manuscript-Based Thesis*. The results are given in the following manuscripts:

Jorge Luis Flores Anato, Dimitra Panagiotoglou, Zoë R Greenwald, Claire Trottier, Maliheh Vaziri, Réjean Thomas, Mathieu Maheu-Giroux. Chemsex practices and pre-exposure prophylaxis (PrEP) trajectories among individuals consulting for PrEP at a large sexual health clinic in Montréal, Canada (2013-2020). *Drug and Alcohol Dependence* 2021 Sep 1; 226:108875. https://doi.org/10.1016/j.drugalcdep.2021.108875.

Jorge Luis Flores Anato, Dimitra Panagiotoglou, Zoë R Greenwald, Maxime Blanchette, Claire Trottier, Maliheh Vaziri, Louise Charest, Jason Szabo, Réjean Thomas, Mathieu Maheu-Giroux. Chemsex and incidence of sexually transmitted infections among Canadian pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013-2020).

The results in this thesis have also been presented at the following scientific conferences:

Flores Anato, JL, D Panagiotoglou, ZR Greenwald, C Trottier, M Vaziri, R Thomas and M Maheu-Giroux. Pratiques de chemsex et trajectoires d'utilisation de la prophylaxie préexposition chez les personnes consultant à la plus grande clinique de santé sexuelle à

Montréal (2013-2019). Poster presentation. *88th Congress of the Association francophone pour le savoir*, virtual conference, May 2021.

Flores Anato, JL, D Panagiotoglou, ZR Greenwald, M Blanchette, C Trottier, M Vaziri, L Charest, J Szabo, R Thomas, M Maheu-Giroux. Chemsex use and incidence of sexually transmitted infections in the l'Actuel pre-exposure prophylaxis (PrEP) cohort in Montréal (2013-2020). Poster presentation. *30th Annual Canadian Conference on HIV/AIDS Research*, virtual conference, May 2021.

Flores Anato, JL, D Panagiotoglou, ZR Greenwald, M Blanchette, C Trottier, M Vaziri, L Charest, J Szabo, R Thomas, M Maheu-Giroux. Chemsex, sexually transmitted infections (STI) and pre-exposure prophylaxis (PrEP): longitudinal analysis of STI incidence in the l'Actuel PrEP cohort (2013-2020). Oral presentation. *17th Annual EBOH Research Day*, Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal (virtual conference), March 2021.

Throughout the main text of the thesis (excluding manuscripts), the personal pronoun "I" is used sparingly to improve the flow of the text. It goes without saying that this work would not have been possible without the invaluable contributions of all co-authors, who are presented in the following section.

Contribution of Authors

JLFA, MM-G, DP, RT and ZRG conceptualized the project. JLFA conducted the background literature review, linked the databases, and performed all analyses. CT, MV, LC and JS organized data collection and management. MB contributed to the interpretation of results for Chapter 5 (manuscript 2). All authors contributed to interpreting results and critically reviewed the manuscripts presented in Chapters 4 and 5. JLFA drafted both manuscripts in Chapters 4 and 5, and all authors revised them for important intellectual content. This thesis was written by JLFA.

Acknowledgements

I would like to start by thanking my supervisor Dr. Mathieu Maheu-Giroux and my co-supervisor Dr. Dimitra Panagiotoglou. Their feedback, support, and encouragement throughout this process has been invaluable. Although the pandemic limited our in-person interactions to only the first half of my degree, they have remained available and supportive despite all the public health limitations and hardships of the past year and a half, and I am immensely grateful for that.

I also want to thank all the staff and clients at *Clinique médicale l'Actuel*, without whom this project would not have been possible. In particular, thanks to Dr. Réjean Thomas, Anne-Fanny Vassal, Claire Trottier and Mali Vaziri for responding promptly to all my queries and for helping me better understand this data. I would like to thank all members from our research group for their feedback throughout this project: Lily Yang, Carla Doyle, Charlotte Delaunay-Lanièce, James Stannah, Salome Kuchukhidze, Rachael Milwid, Katia Giguère, Arnaud Godin, Yiqing Xia and Caroline Hodgins. I am especially grateful to Charlotte, Yiqing and Carla for all of their help with methods and code.

Thanks to the *Canadian Institutes of Health Research* for providing funding for my graduate studies and research. This has enabled me to focus on this important work.

On a personal note, I want to give my sincerest thanks to my parents Jorge and Feymar for all their support and encouragement through this degree and throughout all my education. I am here in part thanks to them and to the complicated but ultimately positive decision of moving to Canada. I also want to thank my partner Alex for her support and her listening.

Table of Contents

List of Tables

Chapter 4

Chapter 5

List of Figures

Chapter 4

Chapter 5

List of Appendices

List of Acronyms and Abbreviations

AIDS	Acquired immunodeficiency syndrome
CAS	Condomless anal sex
CEGEP	Collège d'enseignement général et professionnel
CI	Confidence interval
Crystal meth	Crystal methamphetamine
FMI	Fraction of missing information
gbMSM	Gay, bisexual and other men who have sex with men
GHB	Gamma-hydroxybutyrate
HCV	Hepatitis C virus
HIRI-MSM	HIV Incidence Risk Index for Men who have Sex with Men
HIV	Human immunodeficiency virus
HR	Hazard ratio
IQR	Inter-quartile range
KM	Kaplan-Meier
L'Actuel	Clinique médicale l'Actuel
P3M	Past 3 months
P6M	Past 6 months
P12M	Past 12 months
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
OR	Odds ratio
SDU	Sexualized drug use
STI	Sexually transmitted infection
TDF-FTC	Tenofovir disoproxil fumarate and emtricitabine
UK	United Kingdom
USA	United States of America

Introduction

Despite enormous progress in HIV diagnosis coverage and treatment, many challenges remain to end the HIV/AIDS epidemic. In Canada, gay, bisexual and other men who have sex with men (gbMSM) remain a key population vulnerable to HIV acquisition and transmission [1]. As of 2019, gbMSM still represent over 50% of all new HIV diagnoses in Québec, and diagnosis rates in this population have failed to noticeably decline over the years [2]. HIV elimination in Québec is complex and will require addressing the syndemic (synergistic epidemics) [3,4] of historical and ongoing marginalization of gbMSM, HIV infection, sexually transmitted infections (STIs), and substance use.

The use of illicit substances during sex –referred to as chemsex– has risen in prominence in the past decade, and substance use patterns have shifted significantly [5–7]. These trends are raising public health concerns because chemsex is associated with increases in the incidence of HIV and other STIs [8–12]. In Montréal, it is estimated that between 12–19% of gbMSM report chemsex in the past year [13,14], and there are few interventions and services available for these men. The evidence base supporting a more localized and granular understanding of chemsex practices, the role of chemsex in STI transmission, and its impact on engagement in other prevention services is currently lacking.

Pre-exposure prophylaxis (PrEP) is an important HIV prevention tool for gbMSM at ongoing risk of HIV acquisition, including those who practice chemsex. PrEP has been available in Québec since 2013 and chemsex participation is one of the criteria for eligibility among gbMSM [15,16]. Despite the early availability of PrEP, there is still a lack of evidence regarding how chemsex impacts engagement in PrEP care. This is important to understand: both to ensure PrEP effectiveness and to investigate whether PrEP can serve as a starting point to develop comprehensive HIV prevention programs as some authors have suggested [17].

Objectives

This thesis aims to improve our understanding of chemsex and its role in PrEP use and STI transmission among gbMSM in Montréal. Using data from one of the largest PrEP cohorts in North America, I describe trends in chemsex and PrEP use and examine the effect of chemsex at baseline on STI incidence.

Chapter 1

Literature Review

This chapter first reviews chemsex practices, their prevalence in Canada and Montréal, and the underlying motivations and associated harms. It then briefly describes the epidemiology of sexually transmitted infections (STI) among gay, bisexual and other men who have sex with men (gbMSM) in Canada, with a particular focus on gonorrhea and chlamydia. Lastly, it presents pre-exposure prophylaxis (PrEP) and its connections to chemsex and to STIs.

1.1 Chemsex and sexualized substance use

1.1.1 Defining chemsex: substances and context

Despite a growing body of work related to chemsex and other forms of sexualized drug use (SDU), there is still no agreed upon definition of the practice beyond the intentional use of drugs to enhance sexual pleasure [7]. In contrast with sex under the influence of alcohol, marijuana or cocaine –which may occur after a night out– intentionality is seen as a key element of chemsex [7,18]. However, experiences of chemsex are diverse in the kinds of substances used, the venues where chemsex takes place, and the types of sexual practices involved.

Although the substances used are an important component of the definition, the exact substances that are considered chemsex vary substantially. Crystal methamphetamine (crystal meth), mephedrone and gamma-hydroxybutyrate (GHB) are described as being central to the chemsex phenomenon [5–7,18]. Alcohol and marijuana are almost never included since they have milder effects and are often used without the intent of enhancing sexual experiences. Poppers, cocaine, ecstasy and amphetamines have a longer history of sexualized use within gbMSM communities and are often considered chemsex [5,7,18,19]. However, this is not always the case, and some healthcare professionals have argued that the definition of chemsex should focus specifically on crystal meth, mephedrone and other cathinones, and GHB, as these substances tend to cause the most harm [6,7]. Moreover, some studies focus on crystal meth alone, although these often do so in order to examine both sexualized and non-sexualized use [9,20]. Lastly, heroin and other opioids are rarely included in the chemsex definition. This is likely warranted, as even among gbMSM who practice injection of crystal meth and other substances –considered the most extreme forms of chemsex– the use of opioids is considered too dangerous [21].

Within the ongoing discussions regarding the definition of chemsex, it is important to consider the cultural associations that specific substances have with different venues and scenes. Qualitative studies have shown that chemsex generally takes places within private homes, bathhouses, and sex clubs [21,22]. In Vancouver, qualitative interviews with gbMSM found that ecstasy and cocaine were associated with club and bar culture as well as bathhouses and sex party scenes, but crystal meth was associated specifically with the sex party and chemsex scenes [23]. There is also quantitative evidence to support this: a large survey of nearly 4,000 gbMSM in the UK found that 88% of respondents who reported using crystal methamphetamine, mephedrone, GHB or ketamine reported using it for sex [24]. Chemsex practices are heterogeneous and the specific substances used and sexual behaviours involved may differ greatly depending on the setting and on the previous relationship between participating men [22].

1.1.2 Prevalence of chemsex among gbMSM

It is important to assess the prevalence of chemsex both to know its potential impacts on population-level health outcomes and to estimate how many people may need related services. Despite this, estimates of chemsex prevalence vary substantially across studies, and some studies define chemsex as the use of chemsex-related substances irrespective of context [25–27]. Most studies in Europe and North America found that 10 to 25% of gbMSM report chemsex in the past 12 months (P12M). A recent systematic review showed substantial heterogeneity in prevalence of chemsex due to the multiple definitions of chemsex being used, the different subpopulations being surveyed, and the recall period considered in the survey instruments. Among eight studies that provided an estimate, chemsex prevalence ranged from 3–29%, with studies that sampled within sexual health clinics having estimates in the 17–27% range [18]. A 2016–2017 study of nearly 4,000 gbMSM in England also reported a higher prevalence of chemsex (P12M) among sexual health clinic attendees: 9% among participants recruited via geosocial dating apps vs. 19% among those recruited at sexual health clinics [24].

Canadian estimates of chemsex prevalence among gbMSM fall in the 10–25% range as well. An analysis of the *European Men-who-have-sex-with-men Internet Survey* (EMIS) of 2017 –a large survey of gbMSM that recruited participants in 50 countries, including Canada– estimated that 21.5% of participants in Canada reported ever participating in chemsex (n = 5,165). In Québec (n = 789), 21.4% of participants reported ever participating in chemsex, 12% reported chemsex in the P12M and 6% in the past 6 months (P6M). Notably, this study restricted its definition of

chemsex to stimulants (ecstasy, cocaine, amphetamine/speed, crystal meth, mephedrone and ketamine) and did not consider GHB, which is a commonly used chemsex substance [13].

Studies conducted in Montréal and Toronto have found similar prevalence estimates. Surveys from the 2000s in Montréal, which only reported substance-specific prevalence and used convenience sampling at gbMSM social venues, show that prevalence of SDU in the P6M ranged between 3.6% for crystal meth up to 20.8% for cocaine [28,29]. More recently, 19% of participants in the *Engage Cohort* (n = 1,179) reported chemsex in the P6M for 2017–2018 [14]. Similarly, a study in Toronto found that 18% of participants in the *Gay Strengths Study* (n = 470) reported chemsex in the past 3 months (P3M) [30]. These two studies suggest higher period prevalence of chemsex among gbMSM than reported in the 2017 *European Men-who-have-sex-with-men Internet Survey* (EMIS). This difference could be explained by the focus on urban populations and by the use of sampling methods to gather data on harder-to-reach populations: *Engage* used a respondent-driven sampling design and the *Gay Strengths Study* used rolling recruitment as well as targeted recruitment of racialized minorities.

1.1.2 Motivations for chemsex and associated harms

Motivations for engaging in chemsex are diverse but generally include increased intimacy and pleasure as the main drivers [18,31]. In qualitative interviews of Montréal gbMSM who use or had used crystal meth for chemsex, there was a consensus that the sexual and social dimensions of pleasure were the main motivation for substance use. Other reasons included self-acceptance and an increased sense of connection with partners [20]. Previous research in the UK and the USA similarly highlighted themes of increased arousal, increased sexual intensity and being able to have sex and connect with more partners [18,32]. Studies have also highlighted that chemsex and substance use more broadly may be linked to a desire to fit in and a coping mechanism for some younger gbMSM who are coming to terms with their sexuality [23,31].

While not all chemsex may be inherently problematic, the practice has been linked to various harms including mental health struggles and substance-use related issues [14]. A systematic review by Maxwell et al. highlighted that there is some evidence that chemsex may be associated with loss of social relations and negative mental health outcomes. These outcomes were more frequent among gbMSM who reported frequent chemsex and polysubstance use [18]. Some gbMSM have described overdose episodes and other acute harms during chemsex sessions. The

use of psychoactive substances during sex also raises the complex question of consent, and there is a need for harm reduction interventions that address this issue [21].

Additional to the potential impact of chemsex on mental health and physical health broadly, there is a wide literature on the association between chemsex and sexual practices that increase the transmission risk of HIV and other STIs, such as increases in number of partners and condomless anal sex (CAS). Qualitative studies have found that the practice of chemsex is linked to increases in CAS and to increases in the number of partners, sometimes within the context of sex parties that can span over several days [20,32]. As early as the 2000s, studies in the USA showed an association between SDU and CAS, with the effect estimates being larger for cocaine and amphetamines [33,34]. More recent cross-sectional studies have found chemsex to be associated with higher odds and higher prevalence of CAS, CAS with serodifferent partners or partners of unknown serostatus, and with reporting a larger number of partners [8,14,24,25,35–37].

1.1.3 Association between chemsex and sexually transmitted infections

In addition to the association between chemsex and sexual behaviours that increase STI transmission, research has found a cross-sectional association between chemsex and STIs among gbMSM. Although estimates vary between publications and subpopulations of interest, the literature has consistently shown an association between chemsex and recent or current infection.

Most studies investigating the relationship between chemsex and STIs have used cross-sectional designs, limiting the ability to discern the temporality component. Nonetheless, chemsex has been consistently associated with incident STI diagnoses and recurrent infections [38,39], recent or prevalent STI diagnoses [10,40], and self-reported history of STI [8,11,25,41]. Chemsex and crystal meth use have also been associated with higher rates of HIV seroconversion among HIV-negative gbMSM [9,12]. A recent meta-analysis found that chemsex was associated with an odds ratio (OR) of 2.17 (95% CI: 1.51–3.14) for bacterial STI diagnosis, an OR of 6.07 (95% CI: 2.46–14.98) for hepatitis C virus (HCV) diagnosis and an OR of 3.02 (95% CI: 0.96–9.53) for HIV diagnosis [19]. These numbers likely represent the best estimates available in the literature, although the exact relationship is likely dependant on the chemsex patterns within populations, as well as the specific sexual practices involved during chemsex.

The meta-analysis by Guerra et al. summarizes four pathways through which chemsex may be associated with STI and HIV incidence: (1) disinhibition and impaired decision making due to

the effects of chemsex substances on cognitive ability, (2) physiological changes that increase susceptibility to infection, reduce pain perception or increase libido, (3) SDU being a proxy for dense sexual networks with high STI prevalence, and (4) SDU, STI and HIV transmission forming a syndemic caused by upstream social causes such as poor mental health, stigma, and isolation. The authors mention that these hypotheses may all play a role to varying degrees, although the reviewed evidence only allowed assessment of the first and fourth pathways [19].

1.1.4 Sexually transmitted infections among gbMSM are a public health priority

The association between chemsex and STI incidence among gbMSM has raised public health concerns because this population already bears a disproportionate burden of disease and STI incidence is rising in Canada [42,43]. Between 2008 and 2017, diagnosis rates grew by 39% for chlamydia, 109% for gonorrhea and 167% for syphilis, and the rate of increase for all three infections was higher for men than women [43–46]. Rising incidence among gbMSM is particularly important because rectal STIs are associated with higher transmission risk of HIV [17,47]. Additionally, antibiotic-resistant STI strains are becoming more prevalent, and Québec surveillance data suggests that these are more common among gbMSM and in Montréal [48,49].

1.1.5 Unmet needs among gbMSM who practice chemsex

One proposed hypothesis for the association between chemsex and STI and HIV diagnosis is that chemsex causes impaired decision-making and disinhibition. This leads to sexual practices that would not have happened otherwise, which would increase transmission of STIs including HIV [18,19,32]. While this may be partly the case, qualitative evidence suggests that for some men, the decision not to use condoms is taken prior to substance use. Moreover, some men report being able to reconcile chemsex and safe sex practices such as strict condom use, serosorting, and use of pre-exposure prophylaxis (PrEP) [20,32]. Interventions must therefore acknowledge the diverse values and preferences of gbMSM who practice chemsex and offer services adapted to them, as some authors have argued [7,20,21]. They should also consider where these men are already accessing services.

Men who practice chemsex have been characterized by their high levels of engagement with sexual health services. Evidence from the UK has shown that HIV-negative gbMSM who practice chemsex are more likely to have attended a sexual health clinic compared to men who do not report chemsex. They are also more likely to get tested for STIs and to get more frequent HIV

testing [8,24]. However, men who practice chemsex report not knowing which services to access for their chemsex-related needs and a perceived lack of services tailored to their reality. Although some services for gbMSM who practice chemsex do exist [50–52], these are not widely available. Moreover, qualitative interviews have shown that gbMSM would prefer to access services related to substance use within sexual health clinics [20,21]. In a survey of sexual health clinic attendees in Vancouver, 83% of people with unmet mental health and substance use needs felt comfortable discussing these needs with sexual health clinic staff. Two thirds of the participants were gbMSM, and unmet needs were greater among sexual and gender minorities. Hence, sexual health clinics – which already provide essential services for HIV and STI prevention– present an opportunity for integrated services to address mental health and substance use among gbMSM [53].

1.2 Pre-exposure prophylaxis

PrEP is a biomedical tool to prevent HIV acquisition among populations at ongoing risk of HIV exposure. It has been demonstrated to be highly effective at preventing sexual transmission among gbMSM and transgender women when taken orally [54]. In Canada, it is also recommended for other populations at ongoing risk of HIV acquisition, such as heterosexual couples in which one partner is seropositive without a suppressed viral load and who engage in condomless sex, and people who inject drugs (PWID) and share injection equipment [16].

Oral PrEP can be taken as a daily pill or an intermittent (event-driven) regimen, in which two doses are taken 2–24 hours prior to the sexual contact with potential HIV exposure and a dose taken daily until 48 hours after the last sexual contact. Daily PrEP has shown over 90% efficacy among gbMSM and the intermittent regimen has shown similar efficacy at 86%. The most common form of oral PrEP is a combination of the antiretroviral drugs tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) [54].

1.2.1 PrEP in Canada and Québec

While Health Canada approval of PrEP only occurred in 2016 [55], TDF-FTC for oral daily PrEP has been available in Québec since 2013. Considering the growing scientific evidence in support of PrEP as an HIV-prevention tool and its approval by the USA's Food and Drug Administration in July 2012, Québec's *Ministère de la Santé et des Services sociaux* published interim guidelines in 2013 for the use of daily PrEP for key populations at increased risk of HIV. These guidelines recommended PrEP for seronegative gbMSM who have CAS with partners who

are HIV-positive or of unknown serostatus [56]. Given that TDF-FTC is reimbursable in Québec regardless of HIV status [57,58], this early guidance enabled the introduction of PrEP within the province three years before it was approved by Health Canada in 2016. Following PrEP approval, guidelines were published in 2017 to inform clinicians in Canada on the use of PrEP for populations at ongoing risk of HIV acquisition. These guidelines recommend TDF-FTC as a daily regimen (strong recommendation) or intermittent regimen (weak recommendation). They also note that Health Canada's approval is only for a daily regimen, hence on-demand PrEP is considered "off-label" in Canada [16].

The Québec ministry updated its guidance in 2019 to adjust Canadian guidelines to the Québec context and incorporate new evidence published after 2013. While it mostly endorsed the Canadian guidelines, there were some key differences. For gbMSM, the Canadian criteria for PrEP eligibility are reporting CAS in the P6M and reporting at least one of the following: (1) diagnosis of infectious syphilis or other rectal bacterial STI in the P12M, (2) having used non-occupational post-exposure prophylaxis more than once, (3) an ongoing sexual relationship with an HIV-positive partner with a detectable viral load, or (4) a score of 11 or more in the *HIV Incidence Risk Index for Men who have Sex with Men* (HIRI-MSM) [16,59]. Instead of using the HIRI-MSM, Québec's guidelines add two criteria to this list: reporting the use of psychoactive substances during sex –which would encompass chemsex– and reporting two or more sexual partners in the P6M. These PrEP guidelines also recommend counselling on other HIV/STI prevention strategies and mention that harm reduction interventions with respect to alcohol and substance use should also be encouraged when appropriate, recognizing the need for services addressing chemsex and other forms of substance use [15].

1.2.2 Risk compensation among PrEP users

Although PrEP is highly effective at preventing sexual transmission of HIV, it does not prevent acquisition of other STIs. Because of this, some public health experts have argued that PrEP could cause increases in STI transmission if it leads to discontinuation of other safer sex strategies, a phenomenon referred to as "risk compensation" [60]. This concept remains controversial because it underscores the tension between public health goals and individual values. Moreover, evidence of changes in sexual behaviour and STI incidence following PrEP initiation is limited [61–64], and critics of the concept have pointed out that regular STI screening and secular STI incidence trends could explain the observed increases in PrEP cohorts [65,66].

1.2.3 PrEP as an opportunity for linkage to services

PrEP presents an effective harm-reduction tool for populations at ongoing risk of HIV acquisition. As discussed in section 1.1.5, gbMSM who practice chemsex tend to have higher engagement with sexual health services. They also express a preference for accessing mental health and substance use services at sexual health clinics. Despite chemsex and substance use being a perceived barrier to correct PrEP use, qualitative studies show that gbMSM who practice chemsex are interested in PrEP and can come up with strategies to ensure proper PrEP use [67,68]. Additionally, quantitative studies have shown a lack of association between chemsex or substance use and poor PrEP adherence [69–71]. PrEP thus seems an appropriate HIV-prevention tool for gbMSM who practice chemsex and others at ongoing risk of HIV exposure. From a public health perspective, PrEP could also improve linkage of gbMSM to existing services and presents an opportunity to diversify and expand service offerings at sexual health clinics [17,53].

1.3 Evidence and knowledge gaps

Cross-sectional evidence has established a clear association between chemsex among gbMSM and STI diagnosis (self-reported or laboratory-confirmed), as well as with sexual practices that increase transmission risk of HIV and other STIs. Although chemsex may not be inherently problematic, these associations clearly highlight unmet prevention needs among gbMSM who practice chemsex. Chemsex is therefore a recent but important factor to consider for public health interventions and programs aiming to address rising STI incidence in Canada.

One way to meet the harm reduction needs of gbMSM who practice chemsex –at least for HIV prevention– is PrEP. This is explicitly recognized in Québec guidelines since SDU is one of the possible criteria for PrEP eligibility. Despite concerns among public health experts about risk compensation following PrEP initiation, evidence for or against this phenomenon is inconclusive. Moreover, public health interventions must consider the values, desires, and agency of individuals, and thus risk compensation should not be seen as a reason to limit PrEP availability. PrEP also presents an opportunity to link gbMSM to services and to develop comprehensive programs to address the syndemic of HIV, STIs, mental health challenges and substance use.

Although developing PrEP programs and chemsex services is an urgent priority, key evidence and knowledge gaps remain. First, there is a need for local and contextualized data on chemsex practices in Canadian urban centers such as Montréal. Second, although gbMSM who

practice chemsex have higher engagement in sexual health services, a better understanding of their engagement in the PrEP care cascade is needed. Most importantly, a better and more precise understanding of how chemsex affects STI transmission is needed. Most studies on the chemsex-STI relationship have been cross-sectional and have not examined in detail the role of substance use patterns. To address these questions, this thesis leverages seven years of data from one of the largest PrEP cohorts in North America, as described in the following chapter.

Chapter 2

Study Objectives

The overarching aim of this thesis is to improve our understanding of the evolving patterns of chemsex practices in Montréal and their impact on STI transmission among gbMSM and transgender women using PrEP . This was achieved through two specific objectives:

1. **Objective 1:** describe the chemsex patterns and trends over time and the impact of chemsex on trajectories of PrEP prescription, initiation, and discontinuation, and
2. **Objective 2:** estimate the impact of chemsex on incidence of gonorrhea and chlamydia in a cohort of PrEP users, investigate whether this effect varies for different forms of chemsex, and examine whether certain sociodemographic factors are effect modifiers.

Transgender women were included as their sexual practices may be comparable to those of gbMSM if they are eligible for PrEP. However, it must be noted that they face challenges in society that are distinct from those faced by gbMSM.

Chapter 3

Study Methodology

3.1 Study setting

Clinique médicale l'Actuel (l'Actuel) is a major sexual health clinic in Montréal, serving a clientele composed mostly of gbMSM and specializing in STI and HIV prevention and care. The clinic has been offering daily PrEP since January 2011 and intermittent PrEP since March 2015.

The clinic established the *l'Actuel PrEP Cohort* in 2013 to measure the effectiveness of PrEP as an HIV prevention strategy and as a platform for future HIV prevention research. A more detailed description of the cohort and the study protocols can be found elsewhere [58]. Outside the context of this study, this data has also been used to examine linkage to PrEP care for clients with repeated post-exposure prophylaxis use [72] and risk compensation after PrEP initiation [62].

Clients interested in PrEP are first scheduled for a baseline consultation with a nurse and a doctor to discuss PrEP needs and assess eligibility. During the consultation, clients complete a questionnaire on their sociodemographic profile, sexual health, and substance use. They also undergo a clinical workup, including testing for STIs and HIV, in accordance with Québec recommendations for PrEP [15].

Those who receive a PrEP prescription have a first follow-up visit after one month and regular follow-up visits every three months afterwards. Follow-up visits consist of renewal of the PrEP prescription and a questionnaire on PrEP adherence, side effects, and sexual behaviours. Clients also undergo STI screening and receive counselling to encourage safe sex practices, including condom use. Clients may also use the clinic's STI testing services outside of the scheduled follow-up visits (e.g., if they experience symptoms or were notified by a partner).

3.2 Study population

For both objectives, all adult (≥18 years of age) gbMSM and transgender women who provided written consent, were seronegative for HIV at baseline, and consulted for PrEP at l'Actuel between January 1, 2013 and May 31, 2020 were included. The database includes follow-up visits up to June 30, 2020; follow-up consultations were lagged by one month to allow for sufficient time for the first follow-up for those consulting up to May 31, 2020. Cisgender and

transgender men were considered gbMSM if they (a) identified as homosexual, bisexual, or another sexuality which would include attraction to men (e.g., pansexual, queer) or (b) reported sex with a man in the P12M. All clients who self-identified as transgender women were included. Transgender women were included in the study because some of their risk factors may be comparable to those of gbMSM if they are eligible for PrEP.

The analyses of PrEP discontinuation for the first objective (section 3.4.2) were restricted to clients who reported PrEP initiation within 180 days of their baseline consultation. For the second objective (section 3.4.4), the population was restricted to clients with at least one follow-up visit within 180 days following their initial consultation. All longitudinal analyses were restricted to the first two years following PrEP initiation. This was done because chemsex participation was only reported at baseline, and previous studies suggest there is little within-person change in chemsex practices within this timeframe [73].

3.3 Key definitions

3.3.1 Exposure definitions

The main exposure of interest was chemsex reported at the first visit, which was operationalized using data from the baseline questionnaire. At this initial visit, clients were asked "*In the past 12 months have you had sexual relations under the influence of one or more of the following*," followed by a list of substances. There was no information on the mode of delivery (e.g., smoking, injection or "slamming"). I defined chemsex as reporting sexual relations while under the effect of ecstasy, cocaine, GHB, crack, crystal meth, or ketamine in the P12M. Other substances reported were alcohol, cannabis, poppers, opioids, and heroin, which were not classified as chemsex. GHB, crystal meth and ketamine were included since they are canonical chemsex substances [5,7]. In addition, ecstasy, cocaine, and crack were included, as these are often included in the chemsex definition [5,18] and have been considered in other studies on chemsex in Canada [13,14]. Given the phrasing of the question, it is possible that some clients in the chemsex group did not use drugs specifically to enhance their sexual experience (hence lacking the intentionality of chemsex). This issue would primarily affect clients who reported only ecstasy, cocaine, and/or crack, because GHB, crystal meth and ketamine are used primarily for chemsex among gbMSM [24].

Polysubstance use was defined as reporting ≥2 chemsex substances in the P12M, and an alternative definition of ≥3 was also considered in objective 1. Similar definitions of polysubstance use have been used in previous studies [40,41,74]. The questionnaire did not explicitly ask whether substances were taken together.

3.3.2 Objective 1 outcome definitions

Information from the baseline and follow-up questionnaires was used to operationalize the following definitions related to PrEP trajectory:

- *PrEP prescribed:* a client who (1) had PrEP listed as "recommended" in their file, (2) had a continuous or intermittent PrEP regimen noted in their initial visit or (3) came to a follow-up visit and had a reported PrEP prescription. This definition was used to capture a small proportion of clients who received a prescription after an initial consultation in which PrEP was not prescribed.
- *Initiated PrEP:* reporting PrEP use in at least one follow-up.
- *Discontinued PrEP:* reporting having stopped using PrEP or not coming to a follow-up visit in more than 180 days (the longest a PrEP prescription can be filled for). This definition was used regardless of the PrEP regimen recommended at baseline.
- *Active on PrEP after one year:* having at least 365 days of uninterrupted follow-up (i.e., no discontinuations) after initiating PrEP.

3.3.2 Objective 2 outcome definitions

For gonorrhea and chlamydia infection, a positive diagnosis was defined as a positive nucleic acid amplification test. The database distinguished between swab samples (for rectal and throat infections) and urine samples (for urethral infections). For HCV seroprevalence, prior history of infection was defined as a positive antibody test. Incident HCV infections were defined as an HCV-antibody positive test for clients with a negative HCV antibody test at baseline (seroconversion).

For the baseline prevalence of gonorrhea and chlamydia infection and HCV seroprevalence, tests for each client were retrieved for the date of their baseline consultation or up to two months prior. For gonorrhea and chlamydia incidence, all tests between the baseline consultation (exclusive) and the censoring date for each individual were retrieved. For HCV

incidence, all tests that occurred up to two years after the baseline consultation (exclusive) were retrieved.

3.4 Statistical analyses

Information from the baseline questionnaire was used to describe the sociodemographic characteristics, sexual behaviour, and self-reported STI history of clients consulting for PrEP. Apart from self-reported STI history (which asked about any prior infection), all questions on sexual behaviours were concerned with the past year. All answers were self-reported. All variables were presented as they were asked in the questionnaire [58], except for condom use in P12M, which was categorized (0–25%, >25–50%, >50–75%, >75–100%). This was believed to be more appropriate because preliminary analyses showed clustering of responses around common percentages (e.g., 50%, 75%, 90%) and because it is likely that the percentage reported represents a client's best guess and not an accurate measurement of the proportion of sexual encounters in which a condom was used.

3.4.1 Chemsex trends and patterns (objective 1)

To examine how chemsex practices have changed over the years, temporal trends in the prevalence of chemsex, polysubstance use, and the use of specific substances were examined. As a supplementary analysis, I performed regression-based standardization to examine whether temporal trends in chemsex prevalence were affected by the sociodemographic profile of clients consulting for PrEP, since approval of PrEP by Health Canada in 2016 may have impacted who was consulting for PrEP [55,58]. Confidence intervals (CIs) were constructed using the Bootstrap method, resampling 1,000 times for each prevalence estimate. This standardization method works as follows: for a given year, a logistic regression model is fit with chemsex as the outcome and age, education, and income as predictors. The resulting coefficients are used to predict the individual probability of reporting chemsex for all clients in the reference year (2019 in this case). The standardized prevalence is then computed by taking the mean of all individual probabilities. Thus, this method estimates the chemsex prevalence that would have been observed in the year of interest if the sociodemographic profile of clients consulting in that year had been the same as the reference year. The predictors that were used were:

- age, categorized in three groups: 18–35, 36–50, >50 years old;
- education, dichotomized: post-secondary education, and secondary or less; and

- income (in $CAD), categorized into four groups: ≤$35,000, $35,001–$55,000, $55,000–75,000, and >$75,000.

In the dataset, age was available as a continuous variable. Education and income were coded into four and six levels respectively (education values were university, CEGEP, high school, and primary school; see section 3.4.4 for all income levels). The variables were categorized as described above to ensure that, for each variable, all values were represented in years with few consultations (i.e., 2014 and 2020). Clients with missing values for education and income were retained in the analysis using the missingness indicator method [75]. This analysis excluded 2013 because very few clients consulted during this year (<30), which caused the resampling algorithm to come up with resampling instances in which some variables' values were not represented (and thus coefficients could not be estimated).

3.4.2 PrEP trajectories (objective 1)

To examine how engagement in the PrEP care cascade differed between clients who reported chemsex at baseline and those who did not, I examined PrEP trajectories and persistence. This analysis focused only on the first two years following the baseline visit because chemsex data was only available at baseline (as mentioned in section 3.2) and because individuals are not expected to continue using PrEP indefinitely if their risk profile changes [76].

PrEP trajectory was defined as the proportion of clients who (1) were prescribed PrEP, (2) initiated PrEP and (3) were still using PrEP one year after initiation. For PrEP persistence, Kaplan-Meier (KM) curves were used to compare time to PrEP discontinuation between clients who reported chemsex at baseline and those who did not, restricting to clients who reported initiation within 180 days of their baseline consultation [77]. The date of PrEP initiation was defined as the date of the baseline visit unless the client reported starting PrEP at a later date. The event date for PrEP discontinuation was either (1) the date of self-reported PrEP stop or (2) the date of the last follow-up visit included in the analysis (i.e., the last visit in the database or the last visit before a gap in follow-up of over 180 days). Clients were censored if their last follow-up was 180 days or less from the end date (June 30, 2020) and they had not reported discontinuation at this visit.

Two stratified analyses were done to further examine differences in PrEP trajectory and persistence associated to chemsex. To examine if the results were confounded by differences in PrEP regimen prescribed between groups, PrEP trajectories and the KM curves were stratified by

PrEP regimen prescribed at baseline. To test whether polysubstance use had a different association with PrEP use than chemsex, PrEP trajectories and KM curves were examined using a chemsex variable that was trichotomized as no chemsex, chemsex (1 substance) and polysubstance use (≥2 substances).

The KM curves for PrEP persistence were supplemented by two additional analyses. First, clients who were included in the PrEP discontinuation analysis were compared to those who were excluded using descriptive statistics. Second, an adjusted survival curve was estimated by first fitting a Cox proportional hazards model and then using it to estimate the adjusted survival curves for the whole population using the method described by Therneau and Grambsch. One drawback of this approach is the lack of CIs due to the complexity of estimating the variance of these curves [78]. The regression model was adjusted for age, education, and income, as described in section 3.4.1, as well as year of baseline consultation (treated as a categorical variable) and PrEP regimen (dichotomous, daily vs intermittent). Clients with missing values for education and income were retained in the analysis using the missingness indicator method [75].

For chemsex-related prevalence estimates and PrEP trajectories, uncertainty was summarized using 95% CIs constructed using the Clopper-Pearson method for proportions.

3.4.3 Multiple imputation procedure for education and income (objective 2)

Given the real-world clinic-based setting of data collection, many self-reported measures in the dataset have missing data. This reflects reporting biases (i.e., clients who prefer to not disclose certain information) but also the high-volume nature of the clinic's services, which can result in some information not being systematically collected in questionnaire forms [58].

For this study, education and income were the only variables used in regression analyses that had missing data. This was handled using multiple imputations by chained equations. In preliminary analyses using 5 imputations, the highest fraction of missing information (FMI) was estimated to be 0.18 for the education*chemsex interaction term in the regression model for effect modification by education. I thus chose to perform 12 imputations for the final analysis, in line with recommendations by White and colleagues [79].

The predictors used in the multiple imputation were the chemsex exposure (binary indicator), polysubstance use (binary indicator), event indicator for the primary outcome of gonorrhea or chlamydia diagnosis, cumulative hazard for the primary outcome (estimated using

the Nelson-Aalen estimator) and all confounders included in the regression models (i.e., age, education, income, PrEP regimen at baseline, and year of initial consult).

Education and income were imputed separately for the main analyses and for the reclassified variables used in effect modification analyses. Education was modelled using a polytomous or unordered logistic regression (main analyses) and logistic regression (effect modification analysis). Both income variables were modelled using proportional odds regression.

3.4.4 Impact of chemsex on STI incidence (objective 2)

I examined the impact of reporting chemsex at baseline on incidence of gonorrhea and chlamydia using survival analysis, focusing on the two years following PrEP initiation and using all tests available in this timeframe. Follow-up started at the initial PrEP consultation and clients were censored at (1) their last follow-up visit, (2) the last visit prior to a temporary PrEP discontinuation (defined as a gap in follow-up of >180 days) or (3) after two years of follow-up. Three event dates were considered: date of first diagnosis for either gonorrhea or chlamydia at any site (primary outcome), date of first diagnosis of gonorrhea (any site), and date of first diagnosis of chlamydia (any site). An additional analysis stratified each STI by sample type. The database distinguished between swab samples (rectal and throat infections) and urine samples (urethral infections).

For all three outcomes, KM curves were used to compare cumulative STI incidence between the chemsex and the no-chemsex groups [77]. Cox proportional hazards regression was used to estimate the effect of chemsex at baseline on time to first STI diagnosis. The proportional hazards assumption was verified by plotting the log cumulative hazard for the chemsex and no-chemsex group [77]. For each of the three outcomes, I fit a univariable model and a model adjusted for the following sociodemographic confounders:

- age, categorized in seven groups: 18–25, 26–30, 31–35, 36–40, 41–45, 46–50, and >50 years old;
- education, categorized into three levels: university, CEGEP, and secondary or less;
- income (in $CAD), categorized into six groups: ≤$10,000, $10,001–$20,000, $20,001–$35,000, $35,001–$55,000, $55,001–$75,000, and >$75,000;
- PrEP regimen at baseline: continuous or intermittent; and
- Year of entry into the cohort: 2013–2014, 2015, 2016, 2017, 2018, 2019–2020.

Age was categorized as described to make similarly sized age groups with consistent intervals. The income variable used the categories available in the dataset (the questionnaire had six possible answers for income). Education and year of entry into the cohort were regrouped due to sample size reasons (very few people with primary education consulted at l'Actuel and there were few consultations before 2015 and in 2020 for the available data). Since the number of partners and condom use may be in the causal pathway for the chemsex-STI relationship [19], these variables were not included in the regression models. Missing values for education (n = 486; 23%) and income (n = 378; 18%) were handled using multiple imputations and estimates from 12 imputations were pooled using Rubin's rules (detailed in section 3.4.3) [79,80].

To present an effect estimate on the absolute scale, the risk difference in STI diagnosis at 12 months was estimated as recommended by Austin [81]. Briefly, a Cox model is used to predict the probability of an incident STI diagnosis $1 - Pr(survival)$ after 12 months for each individual. This is done twice, once setting the exposure to 1 ("chemsex") and then setting the exposure to 0 ("no chemsex"). The predicted absolute risks in each group (defined as the mean of all predicted probabilities) are then used to compute the estimated marginal absolute risk difference. CIs for this risk difference were constructed using a multiple imputation-Bootstrap procedure as recommended by Schomaker and Heumann, using 1,000 Bootstrap replicates [82]. This scheme involves Bootstrapping the estimated risk difference for each imputed dataset, then using the Bootstrap distributions to compute the within- and between-imputation variance. The Bootstrap variance estimates are then used to estimate 95% CIs using Rubin's rules.

I also investigated the role of polysubstance use and of specific substances in the chemsex-STI relationship. For polysubstance use, KM curves were estimated, and an additional regression model was fit with a trichotomized chemsex variable: no chemsex (reference), chemsex with only one substance, and polysubstance use. A similar analysis was performed for each substance (only using KM curves), in which chemsex was stratified into individuals who reported one specific substance and those who reported any of the other five.

To explore potential heterogeneity in the effect of chemsex, effect modification by sociodemographic factors was investigated using the framework proposed by Li and Chambless for time-to-event outcomes using Cox proportional hazards regression [83]. Regression models for the main outcome were fit including product terms between chemsex and either age, education, or income. Results were presented as suggested by Knol and VanderWeele [84]. For sample size

reasons and because preliminary analyses using all the categories described previously in this section showed similar coefficients between some groups, the variables were regrouped as follows:

- age was trichotomized: 18–35, 36–50, >50 years old;
- education was dichotomized: post-secondary education, and secondary or less; and
- income (in $CAD) was trichotomized: ≤$35,000, $35,001–75,000, and >$75,000.

3.5 Statistical software

All analyses were performed with R 3.6.2 [85]. Survival analysis was performed using the packages *survival* and *survminer* [86,87]. Multiple imputation was performed using the *mice* package [88]. A full list of the packages used can be found in the appendix.

3.6 Ethics

Ethics approval was obtained through the *Veritas Institutional Review Board* and secondary data analyses conducted as part of this thesis was provided by the *Institutional Review Board* of McGill University (IRB Study Number A12-E84-18A, amended on April 21, 2020).

Chapter 4

Study Results (Manuscript 1)

The first manuscript answers objective 1 of this thesis and describes chemsex practices, temporal trends in chemsex and polysubstance use, and PrEP trajectories for all gbMSM and transgender women who consulted for PrEP at l'Actuel. This manuscript has been published in *Drug and Alcohol Dependence*.

> **Jorge Luis Flores Anato**, Dimitra Panagiotoglou, Zoë R Greenwald, Claire Trottier, Maliheh Vaziri, Réjean Thomas, Mathieu Maheu-Giroux. Chemsex practices and pre-exposure prophylaxis (PrEP) trajectories among individuals consulting for PrEP at a large sexual health clinic in Montréal, Canada (2013-2020). *Drug and Alcohol Dependence* 2021 Sep 1; 226:108875. https://doi.org/10.1016/j.drugalcdep.2021.108875.

Chemsex practices and pre-exposure prophylaxis (PrEP) trajectories among individuals consulting for PrEP at a large sexual health clinic in Montréal, Canada (2013-2020)

Jorge Luis Flores Anato[1], Dimitra Panagiotoglou[1], Zoë R Greenwald[2,3], Claire Trottier[2], Maliheh Vaziri[2], Réjean Thomas[2], Mathieu Maheu-Giroux[1*]

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

[2] Clinique médicale l'Actuel, Montréal, QC, Canada

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

***Corresponding author**:

Mathieu Maheu-Giroux, ScD

Department of Epidemiology, Biostatistics, and Occupational Health

School of Population and Global Health, McGill University

1020 Pine Avenue West, Montréal, QC, Canada

H3A 1A2

E-mail: mathieu.maheu-giroux@mcgill.ca

Phone: (+1) 514-398-5110

Abstract

Introduction: Chemsex among gay, bisexual and other men who have sex with men (gbMSM) has raised public health concerns because of its association with sexual behaviours that can increase transmission of sexually transmitted infections, including HIV. Pre-exposure prophylaxis (PrEP) is highly effective at blocking HIV acquisition, addressing important prevention needs among individuals practicing chemsex. This study aims to improve our understanding of chemsex practices and PrEP trajectories of gbMSM and transgender women consulting for PrEP.

Methods: We used data from the PrEP cohort of Clinique médicale l'Actuel, a major sexual health clinic in Montréal. We describe the sociodemographic profile of clients consulting for PrEP, characterize chemsex and polysubstance use trends over time, and evaluate PrEP trajectories using Kaplan-Meier curves.

Results: Among 2,923 clients who consulted for PrEP between 2013–2020 (2,910 cisgender gbMSM, 6 transgender gbMSM, 7 transgender women), 24% reported chemsex in the past year and 13% reported polysubstance use. The most common chemsex substances were ecstasy (14%), GHB (13%), and cocaine (12%). The proportion of clients reporting chemsex and polysubstance use decreased over time. In both the chemsex and no-chemsex group, 73% of clients initiated PrEP. The median time to discontinuation was similar between the chemsex (6.5 months; 95% CI: 5.3–7.2) and no-chemsex group (6.9 months; 95% CI: 6.3–7.5).

Conclusion: Chemsex is not a barrier to PrEP initiation or persistence. However, these results suggest a high prevalence of chemsex among gbMSM consulting for PrEP, highlighting the need for services addressing the intersection of sexual health and substance use for this population.

Keywords

Chemsex; sexualized substance use; pre-exposure prophylaxis; gbMSM; Canada

Word count – 3,695

1. Introduction

Chemsex –a form of sexualized substance use– is defined as the intentional use of illicit substances during sex to enhance pleasure. The exact definition varies, but the most prominent chemsex-related substances are gamma-hydroxybutyrate (GHB), mephedrone, ketamine and crystal meth (Bourne et al., 2014). In Europe and North America, the past decade has seen possible increases in the practice and a shift in the substances reported (Bourne et al., 2014; Maxwell et al., 2019; McCall et al., 2015). These trends have raised public health concerns because chemsex is associated with sexual behaviours such as condomless sex, which could increase acquisition and transmission of sexually transmitted infections (STI) (Blais et al., 2018; Bourne et al., 2015b; Hammoud et al., 2018). Chemsex has also been associated with STI self-report and clinical diagnosis in cross-sectional studies (Guerra et al., 2020; Ottaway et al., 2017; Pufall et al., 2018). STI risks associated with chemsex may reflect the need for better integration of harm reduction services for sexual health and substance use. Existing substance use services generally focus on overdose prevention or reducing the direct harms of injection substance use and do not acknowledge the motivations of gbMSM who engage in chemsex, which include increased intimacy and pleasure (Bourne et al., 2015a; Flores-Aranda et al., 2019).

Within this context, pre-exposure prophylaxis (PrEP) is an important HIV prevention tool for gbMSM who practice chemsex. PrEP is a highly efficacious method of HIV prevention and presents an opportunity to link these men to services such as STI testing and substance use services (Hammoud et al., 2018; Roux et al., 2018). PrEP is available for gbMSM and other key populations at risk of HIV as a daily or intermittent regimen (also termed “on-demand” or “event-driven”). However, studies have highlighted that some gbMSM perceive chemsex as a potential obstacle to correct PrEP use (Closson et al., 2018; Wade Taylor et al., 2014).

In 2013, Québec became the first Canadian province to issue PrEP guidelines. These guidelines were updated in 2019 and provide directions for both daily and intermittent PrEP (Direction générale de la santé publique, 2019,2013; Tan et al., 2017). This early availability could enable a more nuanced understanding of the intersection of chemsex and PrEP, especially since past studies in this area have been limited by their small sample size and restricted timeframe (O’Halloran et al., 2019; Roux et al., 2018). Moreover, while Canadian studies have estimated the prevalence of chemsex and its association with sexual behaviours, a local and contextualized understanding of chemsex practices among gbMSM in urban centres is needed (Blais et al., 2018;

Brogan et al., 2019; Messier-Peet et al., 2018). In order to optimize sexual health and substance use services for individuals who practice chemsex, characterizing the profile of individuals who practice chemsex, the types of substances used, and the impact of chemsex on engagement in other health services is required.

This study aims to improve our understanding of the evolving chemsex practices and PrEP trajectories of gbMSM and transgender women consulting for PrEP in Montréal. Using data from one of the largest sexual health clinic in Montréal over the 2013–2020 period, we (1) describe the sociodemographic profiles and sexual behaviours of clients consulting for PrEP who reported chemsex, (2) examine trends in the main substances reported and polysubstance use, and (3) evaluate PrEP trajectories of prescription, initiation and discontinuation in relation to chemsex.

2. Methods

2.1 Study setting

The *Clinique médicale l'Actuel* (l'Actuel) is a major sexual health clinic in Montréal specialized in HIV care and prevention and STI screening, serving a patient population composed predominantly of gbMSM. L'Actuel has been offering daily PrEP since 2011 and intermittent PrEP since March 2015. (The clinic started offering PrEP based on trial results and interim guidelines published in the USA). In 2013, this clinic established the l'Actuel PrEP Cohort to measure the effectiveness of PrEP as an HIV prevention strategy and as a platform for future HIV prevention research. A detailed description of this cohort and the study protocols can be found elsewhere (Greenwald et al., 2019; Xia et al., 2020). Briefly, clients interested in PrEP have an initial consultation with a nurse and a doctor in which they discuss their needs with respect to PrEP and respond to a questionnaire on their sociodemographic, sexual health and substance use characteristics. The decision regarding the prescribed PrEP regimen (daily or intermittent) is based on a conversation between the healthcare provider and the client. Intermittent PrEP is generally recommended for people who are certain they will be able to take the PrEP double dose prior to sex. Clients who receive a PrEP prescription for either regimen have a first follow-up visit after one month and regular subsequent follow-ups every three months. At each visit, clients renew their prescription and complete a questionnaire on PrEP adherence, side effects and sexual behaviour.

2.2 Study population

This study includes all adult (≥18 years of age) gbMSM and transgender women who provided written consent, were seronegative for HIV at baseline, and consulted for PrEP at l'Actuel between January 1, 2013 and May 31, 2020. We defined gbMSM as cisgender or transgender men who either (a) identified as homosexual, bisexual, or another sexuality which would include attraction to men (e.g., pansexual, queer) or (b) reported having sex with a man in the past 12 months (P12M). All clients who self-identified as transgender women were included. Transgender women were included in the study because some of their sexual practices may be comparable to those of gbMSM if they are eligible for PrEP.

The database includes follow-up visits up to June 30, 2020; follow-up consultations were lagged by one month to allow for sufficient time for the first PrEP follow-up for those consulting up to May 31, 2020. Given that a small proportion of clients had multiple baseline consultations – due to not initiating PrEP or after a prolonged discontinuation– we restricted the database to only one baseline consultation per client. The chosen visit was either the first consultation or the consultation that led to PrEP initiation (Figure 1).

2.3 Key definitions

Using information from baseline and follow-up questionnaires, we operationalized key definitions related to sexualized substance use and PrEP use as follows:

- *Chemsex:* clients were asked "*In the past 12 months have you had sexual relations under the influence of one or more of the following*," followed by a list of substances. There was no information on the mode of delivery (e.g., smoking, injection or "slamming"). We considered chemsex as reporting sexual relations under the effect of ecstasy, cocaine, GHB, crack, crystal meth or ketamine at least once in the P12M. Other substances consumed (alcohol, cannabis, poppers, opioids and heroin) were not classified as chemsex. This definition is consistent with that used by previous studies in Montréal and elsewhere (Bourne et al., 2014; Maxwell et al., 2019; Messier-Peet et al., 2018).
- *Polysubstance use:* we considered two definitions in the context of chemsex – reporting two or more; or three or more chemsex substances in the P12M. The questionnaire did not explicitly ask whether substances were taken together.

- *PrEP prescribed:* a client who (1) had PrEP listed as "recommended" in their file, (2) had a daily or intermittent PrEP regimen noted in their initial visit or (3) came to a follow-up visit and had a reported PrEP prescription. This definition was used to capture a small proportion of clients who received a prescription after an initial consultation in which PrEP was not prescribed.
- *Initiated PrEP:* reporting PrEP use in at least one follow-up visit.
- *Discontinued PrEP:* reporting having stopped using PrEP or not coming to a follow-up visit in more than 180 days. This definition was used regardless of PrEP regimen recommended at baseline.
- *Active on PrEP after one year:* having at least 365 days of uninterrupted follow-up (i.e., no discontinuations) after initiating PrEP.

2.4 Statistical analyses

Sociodemographic characteristics and sexual behaviour variables are presented as they were asked in the questionnaire, except for condom use in P12M, which was categorized (0–25%, >25–50%, >50–75%, >75–100%). We describe trends in chemsex prevalence and PrEP trajectory, defined as the proportion of clients who (1) were prescribed PrEP, (2) initiated PrEP and (3) were still using PrEP one year after initiation. Precision was summarized using 95% confidence intervals (CIs), constructed using the Clopper-Pearson method for proportions. We used regression-based standardization to examine if temporal trends in chemsex prevalence were affected by changes in the sociodemographic profile of clients consulting for PrEP. The model included age (categorized), education (dichotomized) and income (categorized). CIs were constructed using the Bootstrap method, resampling 1,000 times for each estimate.

Kaplan-Meier curves were used to compare PrEP persistence between clients who reported chemsex at baseline and those who did not, restricting to clients who reported PrEP initiation within 180 days of their baseline consultation. The date of PrEP initiation was defined as the date of the baseline visit unless the client reported starting PrEP at a later date. The event date for PrEP discontinuation was either (1) the date of self-reported PrEP discontinuation or (2) the date of the last follow-up visit included in the analysis (i.e., the last visit in the database or the last visit before a gap in follow-up of over 180 days). Participants were censored if their last follow-up was 180 days or less from the end date (June 30, 2020) and they had not reported discontinuation at this

visit. An adjusted survival curve was estimated by fitting a Cox proportional hazards model adjusted for age, education, income, year of baseline consultation and PrEP regimen (all categorized) (Therneau and Grambsch, 2000). To examine if PrEP trajectory or persistence was influenced by the PrEP regimen, we also stratified the analysis of PrEP trajectory and the Kaplan-Meier curves by PrEP regimen prescribed at baseline.

All analyses were performed with R 3.6.2 (R Core Team, 2019). Survival analysis was performed using the packages *survival* and *survminer* (Kassambara et al., 2019; Therneau et al., 2019).

2.5 Ethics

Ethics approval was obtained through the Veritas Institutional Review Board and the Institutional Review Board of McGill University (A12-E84-18A) approved the secondary data analyses presented in this paper.

3. Results

A total of 3,394 clients consulted for PrEP at l'Actuel between January 2013 and May 2020. Of these, 382 (11%) were excluded because consent was not provided, 1 because the individual was under 18 (<1%), 2 because they tested positive for HIV at baseline (<1%), and 86 because the clients were not gbMSM or transgender women (3%), leaving 2,923 individuals included in the analytic sample (Figure 1). Eight clients initiated PrEP at the clinic before 2013 outside of the context of this cohort and are thus not included in the study (Greenwald et al., 2019).

There were 2,142 clients who initiated PrEP, accumulating 2,894 person-years of follow-up. Among clients with a daily PrEP prescription (n = 1,775), the median follow-up time was 12.6 months (IQR: 4.5–27.1) for clients who reported chemsex and 11.0 months (IQR: 4.2–23.5) for those who did not. Among clients with an intermittent prescription (n = 367), the median follow-up time was 15.4 months (IQR: 4.4–25.7) in the chemsex group and 10.2 (IQR: 4.9–23.1) in the no-chemsex group.

3.1 Are there sociodemographic differences between clients who report chemsex and those who do not?

Of the 2,923 clients who consulted for PrEP and were included in the study, most were gbMSM: there were 2,910 cisgender gbMSM, 6 transgender gbMSM and 7 transgender women. The majority of the sample (99%) identified as either homosexual or bisexual. There were similar

proportions in gender identity and sexual orientation between the chemsex group and the no-chemsex group (Table 1).

Among the 13 transgender clients, the median age was 30, 8 clients reported chemsex in P12M (62%) and all 13 received a prescription for daily PrEP. Seven transgender clients initiated PrEP within 180 days of their baseline consultation and one client was still using PrEP after one year of regular follow-up.

Participants who reported chemsex had similar median ages to those not reporting chemsex (median age 33 vs 35 years) and had an annual income distribution with a mode of $35,001–55,000 CAD (Table 1). There was a higher proportion of missing responses for education level (28%) and income (22%) in the no-chemsex group compared to the chemsex group (13% and 9% respectively) (Table 1).

The median number of regular partners in P12M was the same in both groups (median = 2), but the chemsex group had a slightly higher median number of occasional partners in P12M (median = 13) compared to the no-chemsex group (median = 10). The chemsex group reported lower condom use in P12M during both insertive and receptive anal sex. However, clients who reported chemsex were also more likely to report getting tested for HIV at least yearly (58% vs 48%) and more likely to report asking their partners' HIV status "always" or "often" (68% vs 55%). They were also slightly more likely to have previously used post-exposure prophylaxis (36%) as compared to clients not reporting chemsex (32%). Except for condom use during receptive anal sex, there was a higher proportion of non-reporting in the no-chemsex group for all measures related to sexual health (Table 1).

3.2 What are the patterns of chemsex practices reported by clients consulting for PrEP?

One in four (24%) clients who consulted for PrEP reported chemsex in the P12M and 64% reported having had sex under the influence of at least one substance (Figure 2B). Alcohol (49%), cannabis (30%) and poppers (26%) were the most commonly reported substances. The most common chemsex substances were ecstasy (14%), GHB (13%) and cocaine (12%). A smaller proportion of clients reported crystal meth (5%) and ketamine (4%), and few reported crack (<1%) (Figure 2A). Overall P12M intravenous drug use was low, but it was slightly higher among clients who reported chemsex (2%) compared to those who did not report chemsex (<1%) (Table 1).

Polysubstance use (≥2 chemsex substances) was reported by 13% of participants, which is over half of participants reporting chemsex. This was evenly split among those who reported just two substances and those who reported three or more (Figure 2B).

3.3 How has the prevalence of chemsex changed over time among clients seeking PrEP at l'Actuel?

Chemsex reports were highest in 2014 (38%) and lowest in 2019 (10%). Polysubstance use saw a similar decrease between 2015 (21%) and 2019 (6%). There was a slight increase in 2020 in the prevalence of both chemsex and polysubstance use (Figure 2B). The observed trend in chemsex prevalence was robust to regression-based standardization for age, education, and income (Supplementary Figure 1).

Among participants reporting chemsex, the proportion who reported crystal meth decreased over time whereas the proportion reporting cocaine increased. The proportion who reported GHB, ecstasy and ketamine remained relatively stable, but there was a marked drop between 2019 and 2020 in the proportion reporting ecstasy (Supplementary Figure 2B).

3.4 Is chemsex associated with differences in PrEP outcomes and trajectory?

The proportion of consultations that led to PrEP prescriptions and initiations were 97% and 73%, respectively. These were almost identical among clients who reported chemsex as compared to those who did not. The proportion of clients retained in PrEP care after one year was similar across the chemsex (20%) and no-chemsex groups (18%) (Figure 3A). There were no major differences in PrEP trajectory when stratifying by year of baseline consultation (Supplementary Figure 3). The majority of PrEP prescriptions were for daily PrEP, and the proportion of prescriptions for intermittent PrEP was 16% in the chemsex group and 21% in the no-chemsex group (Supplementary Figure 4). In stratified analyses by PrEP regimen, the proportion who initiated (76% vs 79%) and were retained in care after one year (21% vs 20%) were similar between the chemsex and no-chemsex groups for those on daily PrEP. For clients on intermittent PrEP, the proportion that initiated was 65% for both groups, and the proportion retained in care was slightly larger among clients who reported chemsex (20%) compared to those who did not (12%) (Supplementary Figure 5).

Among 1,935 clients who initiated PrEP within 180 days of their initial consultation, there was little difference in the median time to discontinuation by baseline report of chemsex: 6.5 months (95% CI: 5.3–7.2) in the group reporting chemsex compared to 6.9 months (95% CI: 6.3–

7.5) in the group that did not report chemsex in the P12M (Figure 3B). The median time to PrEP discontinuation was similar across groups when stratifying by PrEP regimen at baseline (Supplementary Figure 6). PrEP trajectories and time to discontinuation were also comparable between clients who reported one chemsex substance and those who reported polysubstance use (Supplementary Figure 7). Adjustment for year of baseline consultation, age, education, income and PrEP regimen did not change the relative shape of the survival curves (Supplementary Figure 8). Only 65 clients reported a late PrEP initiation date (i.e., not at their baseline consultation but within 180 days of it).

There were no major differences in age, education, income, number of partners (regular or occasional) between the clients in this analysis and those who were excluded because they initiated PrEP over 180 days after their initial consultation (n = 207). However, those who were excluded received a higher proportion of intermittent PrEP prescriptions (31% vs 16%) and had a lower prevalence of reported chemsex in P12M (20% vs 24%) (Supplementary Table 1).

Table 1: Sociodemographic characteristics and sexual behaviours of clients consulting for PrEP at the Clinique médicale l'Actuel in Montréal, Canada (2013–2020).

	Reported chemsex		**No chemsex reported**		**Total**	
Total	708		2,215		2,923	
Age (median, IQR)	33	(27–41)	35	(29–45)	35	(28–44)
Gender identity (n,%)						
Cis men	700	98.9%	2,210	99.8%	2,910	99.6%
Trans men	3	0.4%	3	0.1%	6	0.2%
Trans women	5	0.7%	2	0.1%	7	0.2%
Sexual orientation (n,%)						
Homosexual	661	93.4%	2,062	93.1%	2,723	93.2%
Bisexual	39	5.5%	139	6.3%	178	6.1%
Heterosexual	3	0.4%	5	0.2%	8	0.3%
Other	3	0.4%	6	0.3%	9	0.3%
Missing	*2*	*0.3%*	*3*	*0.1%*	*5*	*0.2%*
Education (n,%)*						
Primary or secondary	118	16.7%	201	9.1%	319	10.9%
CEGEP	162	22.9%	301	13.6%	463	15.8%
University	334	47.2%	1086	49.0%	1420	48.6%
Missing	*94*	*13.3%*	*627*	*28.3%*	*721*	*24.7%*
Annual income ($) (n,%)						
≤10,000	47	6.6%	133	6.0%	180	6.2%
10,001–20,000	77	10.9%	165	7.4%	242	8.3%

20,001–35,000	107	15.1%	205	9.3%	312	10.7%
35,001–55,000	159	22.5%	419	18.9%	578	19.8%
55,001–75,000	124	17.5%	315	14.2%	439	15.0%
>75,000	131	18.5%	483	21.8%	614	21.0%
Missing	*63*	*8.9%*	*495*	*22.3%*	*558*	*19.1%*
Intravenous drug use in P12M (n,%)						
Yes	16	2.3%	9	0.4%	25	0.9%
Missing	*154*	*21.8%*	*698*	*31.5%*	*852*	*29.1%*
Number of regular partners in P12M						
Median (IQR)	2	(1–3)	2	(1–3)	2	(1–3)
Missing (n,%)	*102*	*14.4%*	*610*	*27.5%*	*712*	*24.4%*
Number of occasional partners in P12M						
Median (IQR)	13	(6–30)	10	(4–20)	10	(5–20)
Missing (n,%)	*77*	*10.9%*	*587*	*26.5%*	*664*	*22.7%*
Condom use in P12M (insertive anal sex) (n,%)**						
0–25 %	123	20.9 %	229	14.0 %	352	15.8 %
>25–50 %	105	17.9 %	191	11.7 %	296	13.3 %
>50–75 %	68	11.6 %	111	6.8 %	179	8.0 %
>75–100 %	229	39.0 %	821	50.1 %	1050	47.1 %
Missing	*63*	*10.7 %*	*287*	*17.5 %*	*350*	*15.7 %*
Condom use in P12M (receptive anal sex) (n,%)**						
0–25 %	91	15.7 %	141	9.3 %	232	11.1 %
>25–50 %	65	11.2 %	130	8.6 %	195	9.3 %
>50–75 %	53	9.1 %	86	5.7 %	139	6.7 %
>75–100 %	187	32.2 %	670	44.4 %	857	41.0 %
Missing	*185*	*31.8 %*	*482*	*31.9 %*	*667*	*31.9 %*
Previous PEP use (n,%)						
Yes	253	35.7%	698	31.5%	951	32.5%
Missing	*50*	*7.1%*	*432*	*19.5%*	*482*	*16.5%*
HIV testing history (n,%)*						
At least twice / year or at least once / year	409	57.8 %	1066	48.1 %	1475	50.5 %
Once / 2 years or once / 5 years	41	5.8 %	136	6.1 %	177	6.1 %
First time	9	1.3 %	28	1.3 %	37	1.3 %
Other	147	20.8 %	314	14.2 %	461	15.8 %
Missing	*102*	*14.4 %*	*671*	*30.3 %*	*773*	*26.4 %*
Asking partner HIV status (n,%)*						
Always or often	484	68.4 %	1213	54.8 %	1697	58.1 %
Rarely or never	113	16.0 %	302	13.6 %	415	14.2 %
No new partners	5	0.7 %	14	0.6 %	19	0.7 %
Missing	*106*	*15.0 %*	*686*	*31.0 %*	*792*	*27.1 %*

CEGEP: *Collège d'enseignement général et professionnel*, Québec's system of post-secondary education which offers pre-university and professional degrees; IQR: inter-quartile range; P12M: past 12 months; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis.

* Answers shown with "or" (e.g., primary or secondary) were separate options in the questionnaire but were regrouped for clarity.

** For condom use variables, the denominator was only clients who reported either insertive or receptive anal sex, hence the numbers here may not add up to the total in the first row

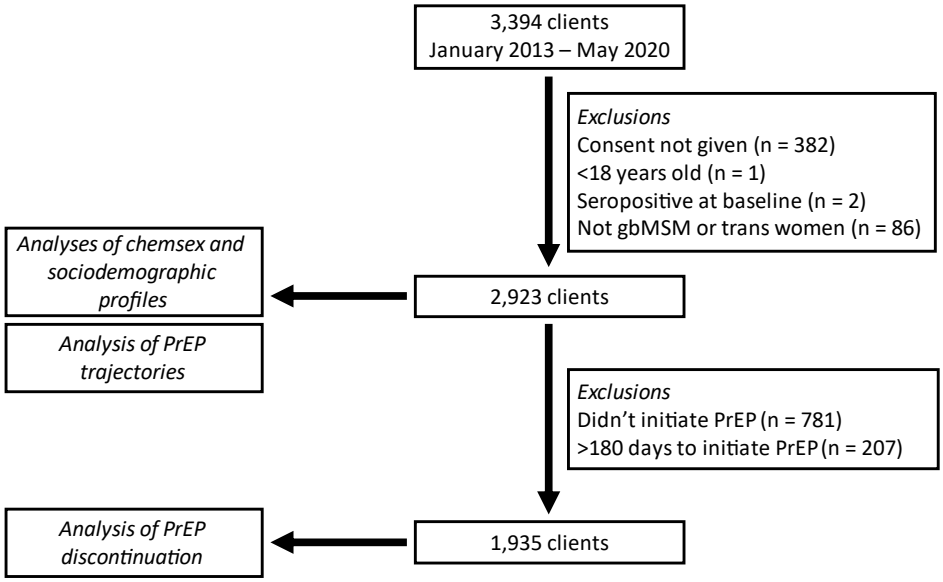


Figure 1: Flowchart of inclusion criteria of clients consulting for PrEP at the *Clinique médicale l'Actuel* in Montréal, Canada. All analyses were conducted with data from 2,923 clients, except for the survival analysis which was done using data from only the 1,935 clients who initiated PrEP on time. gbMSM: gay, bisexual and other men who have sex with men.

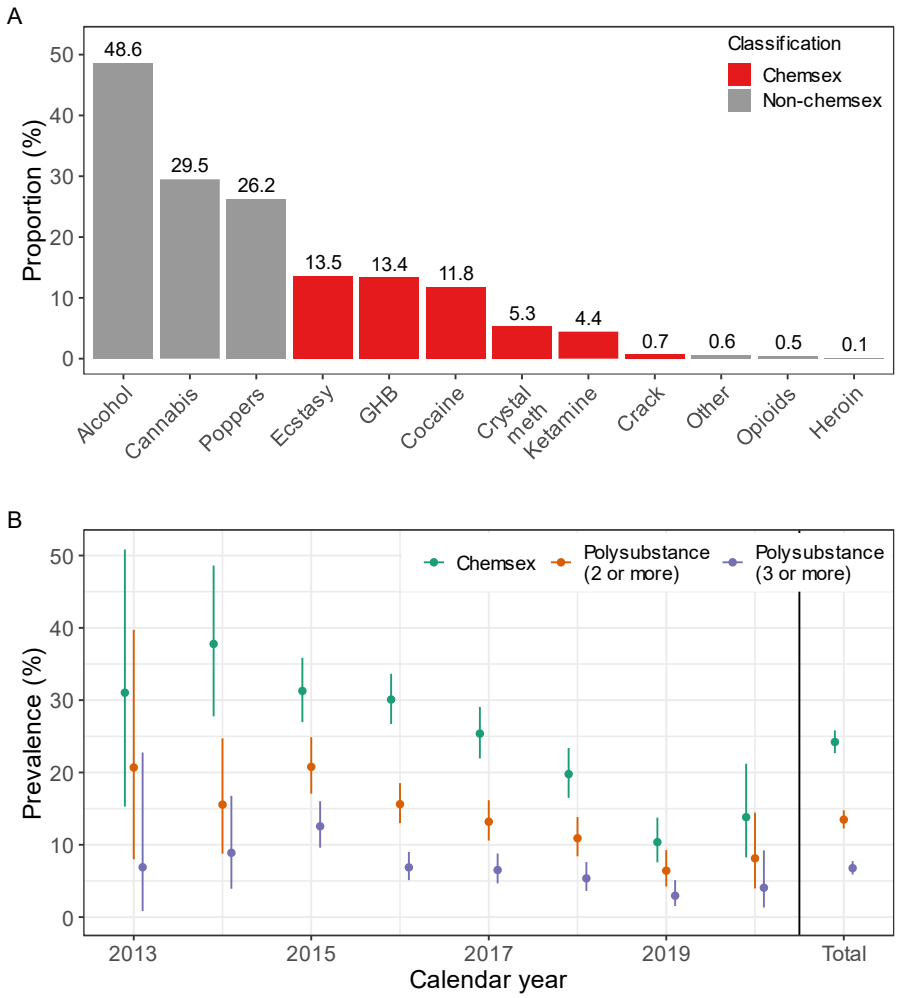


Figure 2: Trends in sexualized substance use among clients consulting for PrEP at the *Clinique médicale l'Actuel* in Montréal, Canada. A) Proportion of participants that reported having used each substance during sex in the past 12 months. B) Prevalence of chemsex and polysubstance use in the past 12 months, stratified by year of baseline consultation. 95% confidence intervals are shown as error bars. GHB: gamma-hydroxybutyrate; PrEP: pre-exposure prophylaxis.

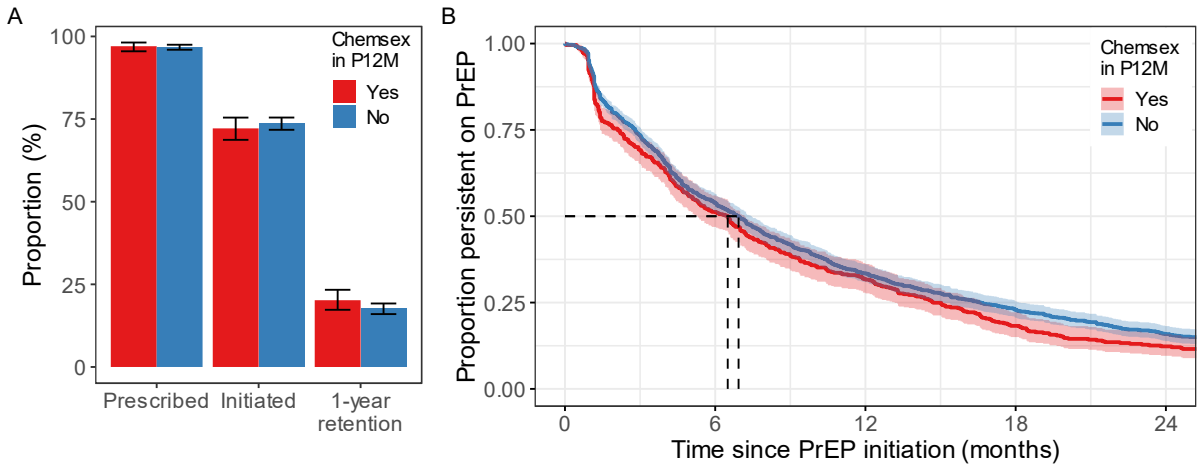


Figure 3: PrEP trajectories of clients consulting for PrEP at the *Clinique médicale l'Actuel* in Montréal, Canada. A) PrEP trajectory of clients who consulted for PrEP stratified by chemsex group. B) Survival curve of time to PrEP discontinuation for clients who initiated PrEP within 180 days of their baseline consultation. 95% confidence intervals are shown as error bars (A) or as a shaded region (B); dotted line in (B) shows median time to discontinuation. P12M: past 12 months; PrEP: pre-exposure prophylaxis.

4. Discussion

Overall, 1 out of every 4 gbMSM who consulted for PrEP over 2013–2020 reported recent chemsex. Importantly, our analyses also indicate that reporting chemsex in P12M at baseline is not a barrier to PrEP initiation nor persistence. These findings suggest that PrEP is meeting a need for harm reduction by offering individuals an additional HIV prevention tool, in line with a combination approach to HIV prevention (Doyle et al., 2021). However, the high prevalence of chemsex and polysubstance use highlights that interventions are needed to reduce some of the potential consequences of these practices for physical, sexual, and mental health.

Among gbMSM and transgender women who consulted for PrEP at l'Actuel between 2013 and 2020, the prevalence of chemsex in the P12M was 24%. Previous studies have found lower prevalence estimates for gbMSM in Montréal (19% in P6M, respondent-driven sampling design) and in Québec (12% in P12M, convenience sample) (Brogan et al., 2019; Messier-Peet et al., 2018). This is in line with findings from a systematic review of chemsex among gbMSM that found that samples from sexual health clinics tend to have higher prevalence estimates (Maxwell et al., 2019). Moreover, the predominance of ecstasy, GHB and cocaine among clients reporting chemsex is similar to what has been previously observed in Montréal and among HIV-negative

gbMSM in England and the Netherlands (Blais et al., 2018; Blomquist et al., 2020; Evers et al., 2019; Sewell et al., 2017).

We observed a temporal decrease in P12M chemsex reports in Montréal, in contrast with trends observed in some European cities (Bourne et al., 2014). However, it is unclear whether this reduction in chemsex prevalence reflects a temporal trend in Montréal or unobserved changes in the composition of who consults for PrEP over time, which could have occurred due to PrEP being officially approved by Health Canada in February 2016 (Health Canada, 2016). Regression-based standardization, however, suggests that the observed trend is robust to adjustments, and prevalence estimates for 2018–2020 are within the range of the studies mentioned above (Brogan et al., 2019; Messier-Peet et al., 2018).

The similar rates of PrEP prescription, initiation, one-year persistence, and PrEP discontinuation suggest that chemsex is not a barrier to PrEP use among study participants. This is in agreement with previous studies that found that gbMSM who report chemsex had similar adherence to PrEP as those not reporting chemsex (O'Halloran et al., 2019; Roux et al., 2018). In previous research identifying chemsex as a potential obstacle to PrEP, participating gbMSM also explored strategies to ensure proper PrEP use (Closson et al., 2018). Moreover, PrEP trajectories were similar for the chemsex and no-chemsex groups even when stratifying by the initial PrEP regimen prescribed (daily or intermittent). Clients who reported polysubstance use also had similar PrEP trajectories to those who reported only one chemsex substance or no chemsex. These results suggest that chemsex does not impede PrEP use or that impediments can be overcome by appropriate strategies.

The low levels of retention after one year and estimated median time to discontinuation should be interpreted with caution. We used a strict definition of discontinuation, which did not capture the fact that clients could stop PrEP temporarily and reinitiate. As previously noted in the PrEP literature, it is not expected that individuals continue using PrEP indefinitely if their risk profile changes (Haberer et al., 2015). Additionally, this definition of discontinuation is less appropriate for clients on intermittent PrEP, for whom follow-up visits will depend on how frequently they need to use PrEP.

The results presented here are strengthened by the large number of clients who completed surveys when consulting for PrEP at l'Actuel and the seven-year span of data collection and

extensive follow-up. Moreover, the baseline questionnaire asked for detailed information on chemsex substances and specifically asked about substance use in relation to sex.

These analyses should also be interpreted with some limitations in mind. Our measurement of chemsex, sociodemographic characteristics and sexual behaviours is based on self-report, which is prone to social desirability bias. Although data on multiple substances was available, there was no measure of chemsex frequency or mixing of substances. Clients were not asked about chemsex during follow-up, which could lead to misclassification (clients who did not report chemsex at baseline but started afterwards and vice-versa). However, this would only impact our analysis of PrEP trajectory. Additionally, one study of temporal trends in chemsex practices saw little within-person change in chemsex practices within two years, hence it is unlikely that there were major changes in practicing chemsex within the analyzed timeframe (Sewell et al., 2019). It is also possible that individuals initiated or continued PrEP use outside of l'Actuel, which we were unable to capture. Lastly, the number of transgender participants was too small to allow for stratified analysis.

5. Conclusions

Despite that one out of four clients consulting for PrEP reported chemsex, this practice is not an obstacle to PrEP initiation or persistence. There are few services addressing the specific needs of people who practice chemsex in Québec. PrEP could be a point of entry to deliver integrated services that address unmet needs that lie at the intersection of substance use and sexual health for gbMSM. Further work is needed to develop such services and to better understand the needs of individuals who practice chemsex.

6. References

Blais, M., Otis, J., Lambert, G., Cox, J., Haig, T., Groupe de recherche Spot, 2018. Consommation de substances en contexte sexuel chez des hommes gbHSH de Montréal : 2009-2016. Drogues, santé et société 17, 76. https://doi.org/10.7202/1062117ar

Blomquist, P.B., Mohammed, H., Mikhail, A., Weatherburn, P., Reid, D., Wayal, S., Hughes, G., Mercer, C.H., 2020. Characteristics and sexual health service use of MSM engaging in chemsex: results from a large online survey in England. Sex Transm Infect. https://doi.org/10.1136/sextrans-2019-054345

Bourne, A., Reid, D., Hickson, F., Torres Rueda, S., Weatherburn, P., 2014. The Chemsex study: drug use in sexual settings among gay and bisexual men in Lambeth, Southwark and Lewisham (Technical Report). Sigma Research, London School of Hygiene & Tropical Medicine, London.

Bourne, A., Reid, D., Hickson, F., Torres-Rueda, S., Steinberg, P., Weatherburn, P., 2015a. "Chemsex" and harm reduction need among gay men in South London. Int J Drug Policy 26, 1171–1176. https://doi.org/10.1016/j.drugpo.2015.07.013

Bourne, A., Reid, D., Hickson, F., Torres-Rueda, S., Weatherburn, P., 2015b. Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: findings from a qualitative study. Sex Transm Infect 91, 564–568. https://doi.org/10.1136/sextrans-2015-052052

Brogan, N., Paquette, D.M., Lachowsky, N.J., Blais, M., Brennan, D.J., Hart, T.A., Adam, B., 2019. Canadian results from the European Men-who-have-sex-with-men Internet survey (EMIS-2017). Can Commun Dis Rep 45, 271–282. https://doi.org/10.14745/ccdr.v45i11a01

Closson, E.F., Mitty, J.A., Malone, J., Mayer, K.H., Mimiaga, M.J., 2018. Exploring strategies for PrEP adherence and dosing preferences in the context of sexualized recreational drug use among MSM: a qualitative study. AIDS Care 30, 191–198. https://doi.org/10.1080/09540121.2017.1360992

Direction générale de la santé publique, 2019. La Prophylaxie Préexposition au Virus de l'Immunodéficience Humaine : Guide pour les Professionnels de la Santé du Québec. Ministère de la Santé et des Services sociaux.

Direction générale de la santé publique, 2013. Avis Intérimaire sur la Prophylaxie Préexposition au Virus de l'Immunodéficience Humaine. Ministère de la Santé et des Services sociaux.

Doyle, C.M., Maheu-Giroux, M., Lambert, G., Mishra, S., Apelian, H., Messier-Peet, M., Otis, J., Grace, D., Hart, T.A., Moore, D.M., Lachowsky, N.J., Cox, J., the Engage Study Team, 2021. Combination HIV prevention strategies among Montreal gay, bisexual, and other men who have sex with men in the prep era: a latent class analysis. AIDS Behav 25, 269–283. https://doi.org/10.1007/s10461-020-02965-4

Evers, Y.J., Liere, G.A.F.S.V., Hoebe, C.J.P.A., Dukers-Muijrers, N.H.T.M., 2019. Chemsex among men who have sex with men living outside major cities and associations with sexually transmitted infections: A cross-sectional study in the Netherlands. PLOS ONE 14, e0216732. https://doi.org/10.1371/journal.pone.0216732

Flores-Aranda, J., Goyette, M., Aubut, V., Blanchette, M., Pronovost, F., 2019. Let's talk about chemsex and pleasure: the missing link in chemsex services. Drugs Alcohol Today 19, 189–196. https://doi.org/10.1108/DAT-10-2018-0045

Greenwald, Z.R., Maheu-Giroux, M., Szabo, J., Robin, J.A.B., Boissonnault, M., Nguyen, V.-K., Thomas, R., 2019. Cohort profile: l'Actuel Pre-Exposure Prophylaxis (PrEP) Cohort study in Montreal, Canada. BMJ Open 9. https://doi.org/10.1136/bmjopen-2018-028768

Guerra, F.M., Salway, T.J., Beckett, R., Friedman, L., Buchan, S.A., 2020. Review of sexualized drug use associated with sexually transmitted and blood-borne infections in gay, bisexual and other men who have sex with men. Drug Alcohol Depend 216, 108237. https://doi.org/10.1016/j.drugalcdep.2020.108237

Haberer, J.E., Bangsberg, D.R., Baeten, J.M., Curran, K., Koechlin, F., Amico, K.R., Anderson, P., Mugo, N., Venter, F., Goicochea, P., Caceres, C., O'Reilly, K., 2015. Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. AIDS 29, 1277–1285. https://doi.org/10.1097/QAD.0000000000000647

Hammoud, M.A., Vaccher, S., Jin, F., Bourne, A., Haire, B., Maher, L., Lea, T., Prestage, G., 2018. The new MTV generation: Using methamphetamine, TruvadaTM, and ViagraTM to enhance sex and stay safe. Int J Drug Policy 55, 197–204. https://doi.org/10.1016/j.drugpo.2018.02.021

Health Canada, 2016. Regulatory Decision Summary - TRUVADA [WWW Document]. URL https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00107 (accessed 2.20.21).

Kassambara, A., Kosinski, M., Biecek, P., Fabian, S., 2019. survminer: Drawing Survival Curves using "ggplot2."

Maxwell, S., Shahmanesh, M., Gafos, M., 2019. Chemsex behaviours among men who have sex with men: A systematic review of the literature. Int J Drug Policy 63, 74–89. https://doi.org/10.1016/j.drugpo.2018.11.014

McCall, H., Adams, N., Mason, D., Willis, J., 2015. What is chemsex and why does it matter? BMJ 351. https://doi.org/10.1136/bmj.h5790

Messier-Peet, M., Herak Apelian, Gilles Lambert, Joseph Cox, 2018. Chemsex & Mental Health in gbMSM in Montreal: Results from Engage Cycle 1.

O'Halloran, C., Rice, B., White, E., Desai, M., Dunn, D.T., McCormack, S., Sullivan, A.K., White, D., McOwan, A., Gafos, M., 2019. Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants. Int J Drug Policy 74, 246–254. https://doi.org/10.1016/j.drugpo.2019.10.007

Ottaway, Z., Finnerty, F., Amlani, A., Pinto-Sander, N., Szanyi, J., Richardson, D., 2017. Men who have sex with men diagnosed with a sexually transmitted infection are significantly more likely to engage in sexualised drug use. Int J STD AIDS 28, 91–93. https://doi.org/10.1177/0956462416666753

Pufall, E.L., Kall, M., Shahmanesh, M., Nardone, A., Gilson, R., Delpech, V., Ward, H., 2018. Sexualized drug use ('chemsex') and high-risk sexual behaviours in HIV-positive men who have sex with men. HIV Med 19, 261–270. https://doi.org/10.1111/hiv.12574

R Core Team, 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

Roux, P., Fressard, L., Suzan-Monti, M., Chas, J., Sagaon-Teyssier, L., Capitant, C., Meyer, L., Tremblay, C., Rojas-Castro, D., Pialoux, G., Molina, J.-M., Spire, B., 2018. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. J Acquir Immune Defic Syndr 79, e69. https://doi.org/10.1097/QAI.0000000000001781

Sewell, J., Cambiano, V., Speakman, A., Lampe, F.C., Phillips, A., Stuart, D., Gilson, R., Asboe, D., Nwokolo, N., Clarke, A., Rodger, A.J., 2019. Changes in chemsex and sexual behaviour over time, among a cohort of MSM in London and Brighton: Findings from the AURAH2 study. Int J Drug Policy 68, 54–61. https://doi.org/10.1016/j.drugpo.2019.03.021

Sewell, J., Miltz, A., Lampe, F.C., Cambiano, V., Speakman, A., Phillips, A.N., Stuart, D., Gilson, R., Asboe, D., Nwokolo, N., Clarke, A., Collins, S., Hart, G., Elford, J., Rodger, A.J., 2017. Poly drug use, chemsex drug use, and associations with sexual risk behaviour in HIV-negative men who have sex with men attending sexual health clinics. Int J Drug Policy 43, 33–43. https://doi.org/10.1016/j.drugpo.2017.01.001

Tan, D.H.S., Hull, M.W., Yoong, D., Tremblay, C., O'Byrne, P., Thomas, R., Kille, J., Baril, J.-G., Cox, J., Giguere, P., Harris, M., Hughes, C., MacPherson, P., O'Donnell, S., Reimer, J., Singh, A., Barrett, L., Bogoch, I., Jollimore, J., Lambert, G., Lebouche, B., Metz, G., Rogers, T., Shafran, S., 2017. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. CMAJ 189, E1448–E1458. https://doi.org/10.1503/cmaj.170494

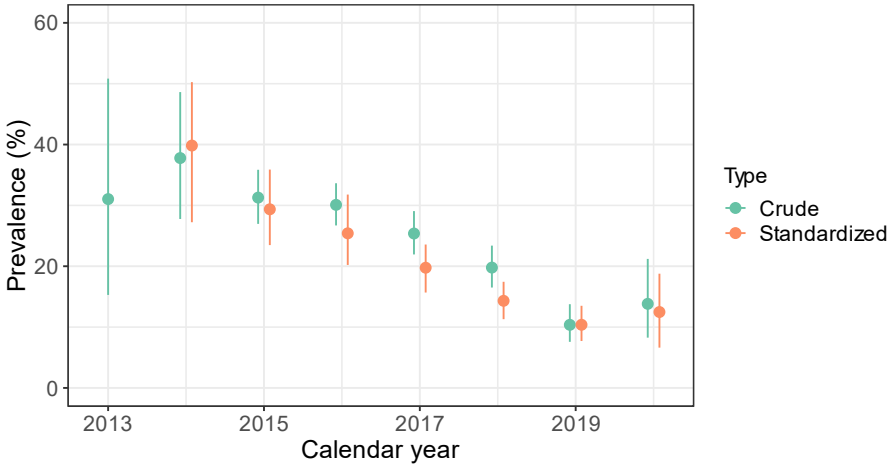
Therneau, T.M., Grambsch, P.M., 2000. Modeling Survival Data: Extending the Cox Model, Statistics for Biology and Health. Springer International Publishing.

Therneau, T.M., Thomas Lumley, Elizabeth, A., Cynthia, C., 2019. survival: Survival Analysis.

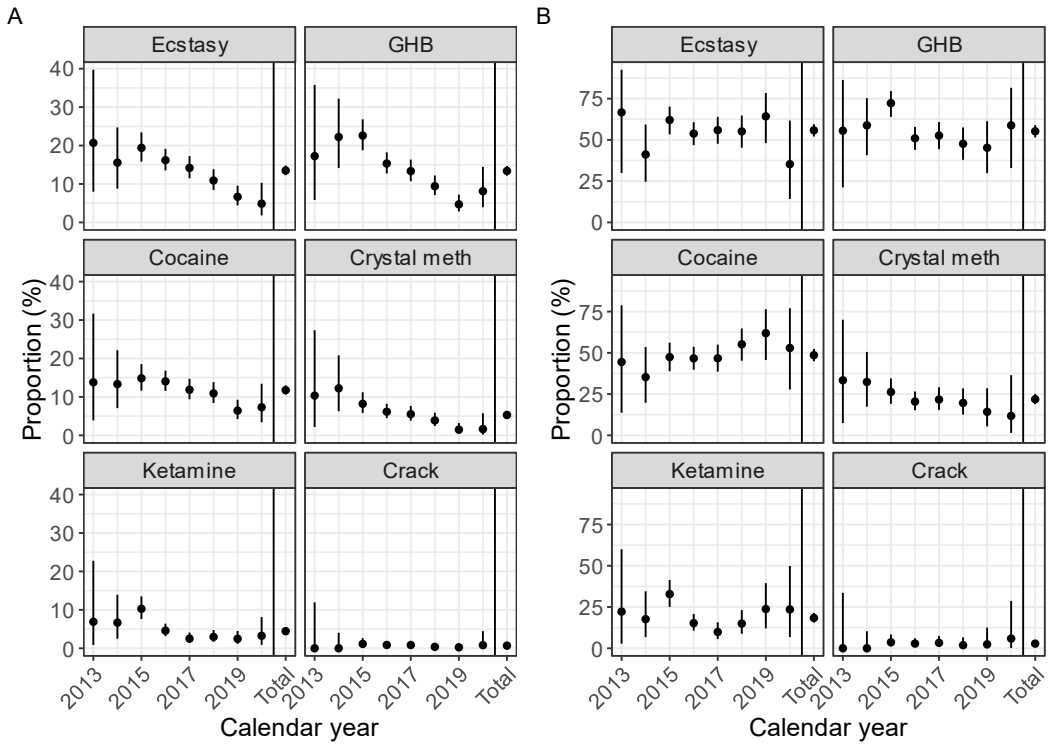
Wade Taylor, S., Mayer, K.H., Elsesser, S.M., Mimiaga, M.J., O'Cleirigh, C., Safren, S.A., 2014. Optimizing Content for Pre-exposure Prophylaxis (PrEP) Counseling for Men Who Have Sex with Men: Perspectives of PrEP Users and High-Risk PrEP Naïve Men. AIDS Behav 18, 871–879. https://doi.org/10.1007/s10461-013-0617-7

Xia, Y., Greenwald, Z.R., Milwid, R.M., Trottier, C., Boissonnault, M., Gaul, N., Charest, L., Landry, G., N. Zahedi, N., Szabo, J., Thomas, R., Maheu-Giroux, M., 2020. Pre-exposure Prophylaxis Uptake Among Men Who Have Sex With Men Who Used nPEP: A Longitudinal Analysis of Attendees at a Large Sexual Health Clinic in Montréal (Canada). J Acquir Immune Defic Syndr 85, 408–415. https://doi.org/10.1097/QAI.0000000000002472

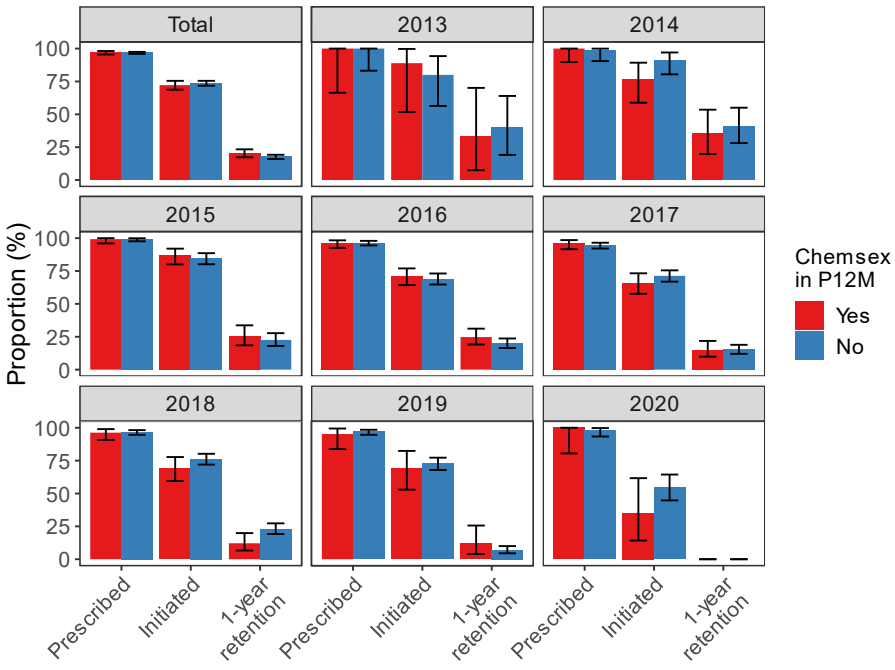
Supplementary results



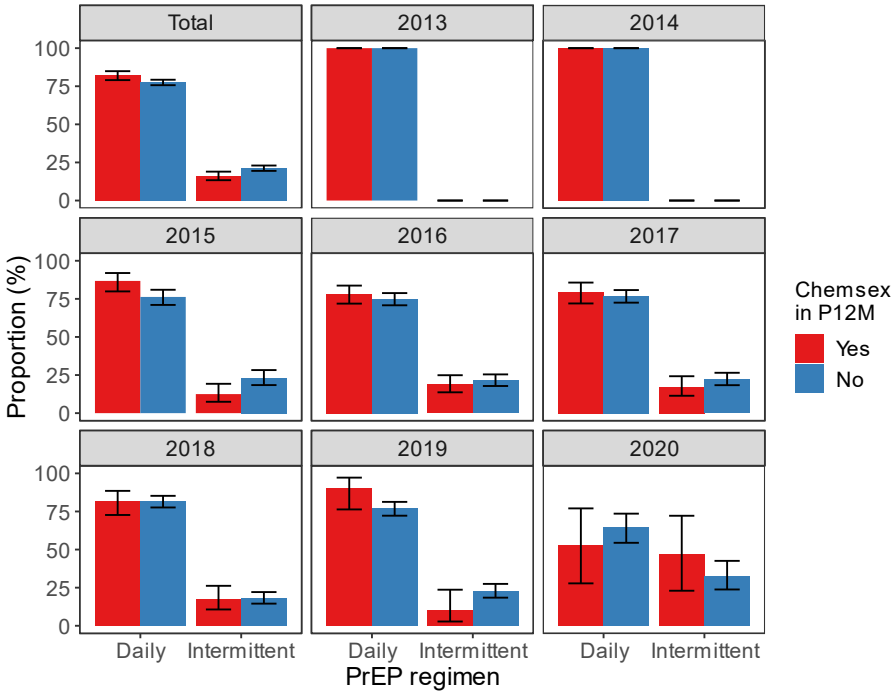
Supplementary Figure 1: Prevalence of chemsex in the past 12 months standardized for age, education and income, stratified by year of baseline consultation. Error bars show 95% confidence intervals, produced using the Bootstrap method for the standardized prevalence (n = 1,000 resampling per year). Reference year is 2019, 2013 was excluded from this analysis due to small sample size (n < 30).



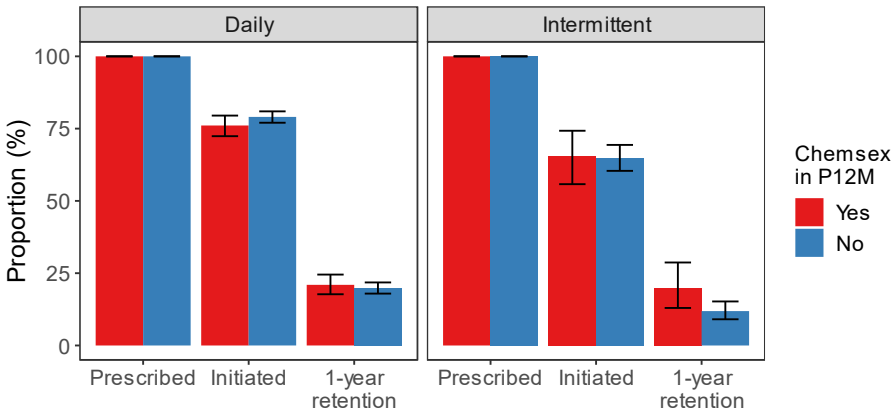
Supplementary Figure 2: Proportion of clients that reported having used each substance during sex in the past 12 months, stratified by year of baseline consultation. A) Proportion among all participants. B) Proportion among participants who reported chemsex. Error bars show 95% confidence intervals. GHB: gamma-hydroxybutyrate.



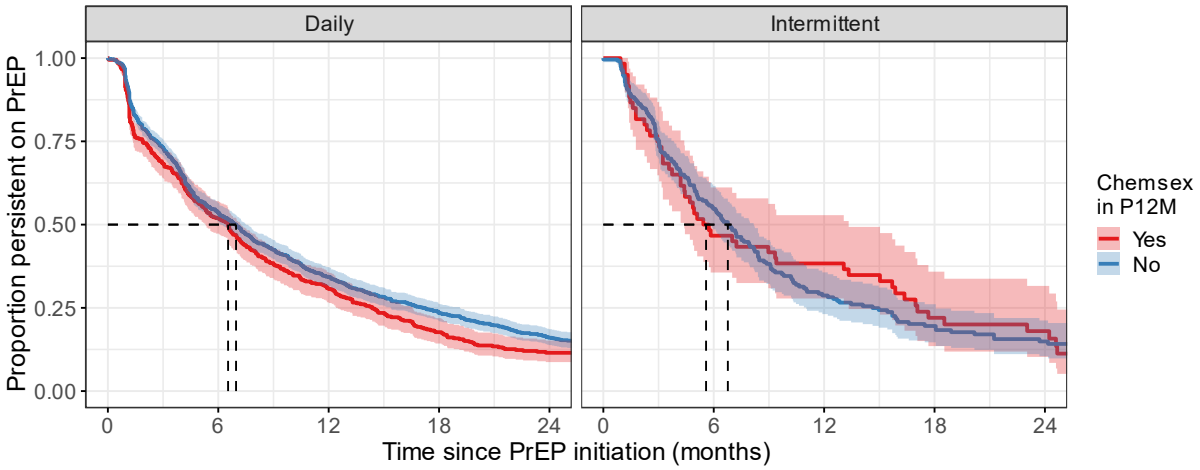
Supplementary Figure 3: PrEP trajectory of clients who consulted for PrEP, stratified by year of baseline consultation. Error bars show 95% confidence intervals. P12M: past 12 months; PrEP: pre-exposure prophylaxis.



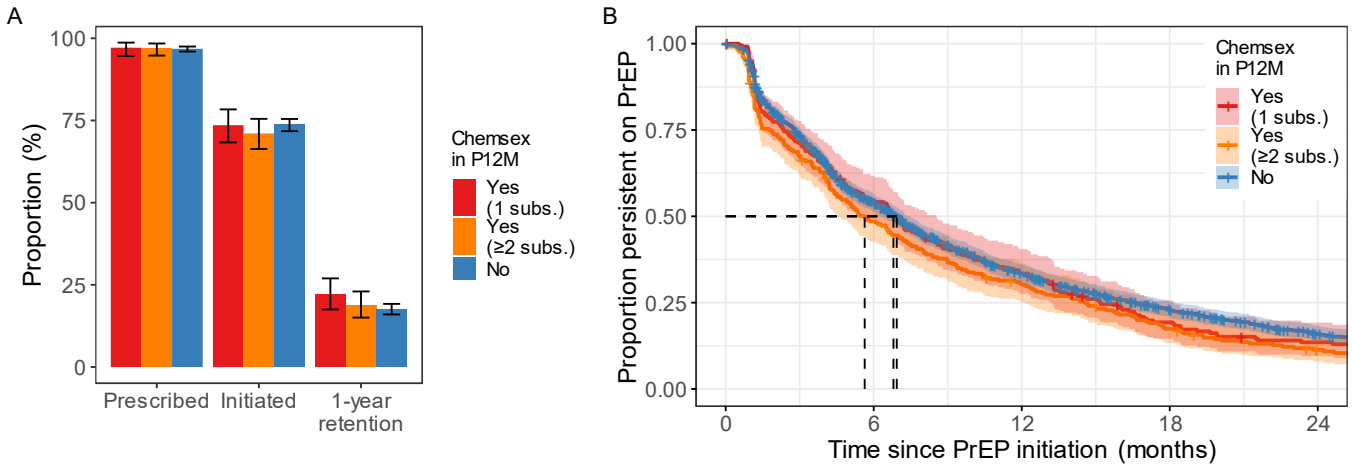
Supplementary Figure 4: PrEP prescriptions by regimen, stratified by year of baseline consultation. Error bars show 95% confidence intervals. P12M: past 12 months; PrEP: pre-exposure prophylaxis.



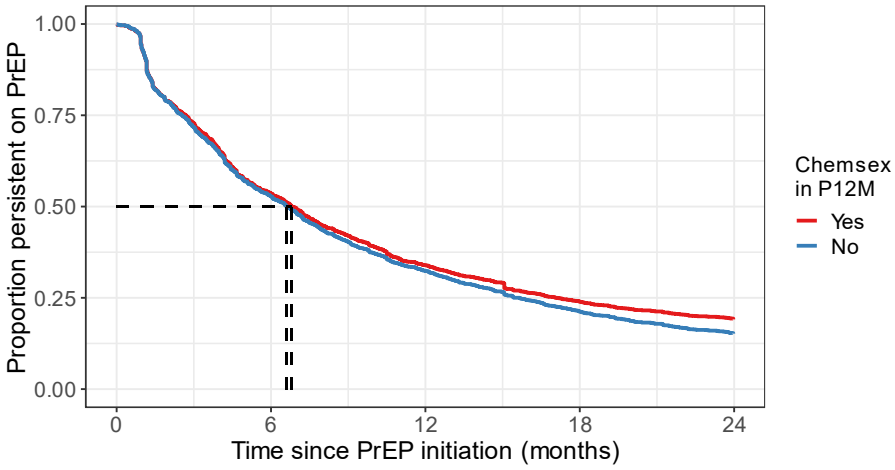
Supplementary Figure 5: PrEP trajectory of clients who consulted for PrEP, stratified by PrEP regimen. Error bars show 95% confidence intervals. P12M: past 12 months; PrEP: pre-exposure prophylaxis.



Supplementary Figure 6: Survival curve of time to PrEP discontinuation for clients who initiated PrEP within 180 days of their baseline consultation, stratified by PrEP regimen. Median time to discontinuation (daily regimen): chemsex: 6.5 months (95% CI: 5.3–7.2); no chemsex: 7.0 months (95% CI: 6.1–7.5). Median time to discontinuation (intermittent regimen): chemsex: 5.6 months (95% CI: 4.4–13.3); no chemsex: 6.8 months (95% CI: 5.7–8.2). Shaded region shows 95% confidence intervals. P12M: past 12 months; PrEP: pre-exposure prophylaxis.



Supplementary Figure 7: PrEP trajectories of clients consulting for PrEP, stratified by reported polysubstance use at baseline. A) PrEP trajectory of clients who consulted for PrEP stratified by chemsex group. B) Survival curve of time to PrEP discontinuation for clients who initiated PrEP within 180 days of their baseline consultation. Median time to discontinuation: chemsex (1 substance): 6.8 (95% CI: 5.6-8.5); chemsex (≥2 substances): 5.6 (95% CI: 4.5-7.2); no chemsex: 6.9 (95% CI: 6.3-7.5). 95% confidence intervals are shown as error bars (A) or as a shaded region (B); dotted line in B shows median time to discontinuation. P12M: past 12 months; PrEP: pre-exposure prophylaxis.



Supplementary Figure 8: Adjusted survival curve of time to PrEP discontinuation for clients who initiated PrEP within 180 days of their baseline consultation. Cox proportional hazards model adjusted for year of baseline consultation, age, education, income and PrEP regimen at baseline. Clients with missing values for education and income were retained in the analysis using the missingness indicator method. P12M: past 12 months; PrEP: pre-exposure prophylaxis.

Supplementary Table 1: Sociodemographic characteristics and sexual behaviours of clients excluded from the survival analysis.

	Included in analysis (started PrEP "on time")		Excluded (started PrEP late)		Excluded (did not start PrEP)	
Total	1,935		207		781	
Age (median, IQR)	36	(29–45)	34	(28–45)	32	(27–41)
Education (n,%)						
Primary	13	0.7%	1	0.5%	3	0.4%
Secondary	196	10.1%	18	8.7%	88	11.3%
CEGEP	295	15.2%	30	14.5%	138	17.7%
University	971	50.2%	106	51.2%	343	43.9%
Missing	*460*	*23.8%*	*52*	*25.1%*	*209*	*26.8%*
Annual income ($) (n,%)						
≤10,000	113	5.8%	14	6.8%	53	6.8%
10,001–20,000	142	7.3%	16	7.7%	84	10.8%
20,001–35,000	200	10.3%	14	6.8%	98	12.5%
35,001–55,000	379	19.6%	38	18.4%	161	20.6%
55,001–75,000	299	15.5%	28	13.5%	112	14.3%
>75,000	443	22.9%	51	24.6%	120	15.4%
Missing	*359*	*18.6%*	*46*	*22.2%*	*153*	*19.6%*
Number of regular partners in P12M						
Median (IQR)	2	(1–3)	2	(1–3)	1	(1–3)
Missing (n,%)	*469*	*24.2%*	*58*	*28.0%*	*185*	*23.7%*
Number of occasional partners in P12M						
Median (IQR)	10	(5–20)	10	(5–20)	10	(4–15)
Missing (n,%)	*432*	*22.3%*	*56*	*27.1%*	*176*	*22.5%*
Chemsex in P12M (n,%)						
Yes	469	24.2%	42	20.3%	197	25.2%
No	1,466	75.8%	165	79.7%	584	74.8%
Recommended PrEP regimen (n,%)						
Daily	1,632	84.3%	143	69.1%	450	57.6%
Intermittent	303	15.7%	64	30.9%	197	25.2%
None	0	0.0%	0	0.0%	64	8.2%
Year of initial baseline consultation (n,%)						
2013	23	1.2%	1	0.5%	5	0.6%
2014	68	3.5%	9	4.3%	13	1.7%
2015	335	17.3%	39	18.8%	64	8.2%
2016	430	22.2%	56	27.1%	212	27.1%
2017	379	19.6%	40	19.3%	180	23.0%
2018	366	18.9%	39	18.8%	136	17.4%
2019	271	14.0%	22	10.6%	112	14.3%
2020	63	3.3%	1	0.5%	59	7.6%

CEGEP: *Collège d'enseignement général et professionnel*, Québec's system of post-secondary education which offers pre-university and professional degrees; IQR: inter-quartile range; P12M: past 12 months; PrEP: pre-exposure prophylaxis.

Chapter 5

Study Results (Manuscript 2)

The previous chapter presented analyses aimed at answering objective 1 of this thesis and described chemsex trends and PrEP trajectories of gbMSM and transgender women who consulted for PrEP. This chapter consists of the second manuscript which aims to answer objective 2. It presents an examination of the chemsex-STI relationship and an investigation into the role of polysubstance use and potential effect modifiers such as age, education, and income. Given that about one third of individuals who consulted for PrEP did not return for follow-up, the study population in this second manuscript is a subset of the study population of the first manuscript. At the time of writing, this manuscript is currently undergoing peer review.

Jorge Luis Flores Anato, Dimitra Panagiotoglou, Zoë R Greenwald, Maxime Blanchette, Claire Trottier, Maliheh Vaziri, Louise Charest, Jason Szabo, Réjean Thomas, Mathieu Maheu-Giroux. Chemsex and incidence of sexually transmitted infections among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013-2020).

Chemsex and incidence of sexually transmitted infections among Canadian pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013-2020)

Jorge Luis Flores Anato[1], Dimitra Panagiotoglou[1], Zoë R Greenwald[2,3], Maxime Blanchette[4], Claire Trottier[2], Maliheh Vaziri[2], Louise Charest[2], Jason Szabo[2], Réjean Thomas[2], Mathieu Maheu-Giroux[1*]

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

[2] Clinique médicale l'Actuel, Montréal, QC, Canada

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

[4] Université du Québec en Abitibi-Témiscamingue, Rouyn-Noranda, QC, Canada

***Corresponding author**:

Mathieu Maheu-Giroux, ScD

Department of Epidemiology, Biostatistics, and Occupational Health

School of Population and Global Health, McGill University

1020 Pine Avenue West, Montréal, QC, Canada

H3A 1A2

E-mail: mathieu.maheu-giroux@mcgill.ca

Phone: (+1) 514-398-5110

Word count: 3,393

Key messages

- Chemsex at baseline is linked to 32% higher hazard of gonorrhea or chlamydia diagnoses among gbMSM using PrEP in a large cohort in Montréal.
- Despite high STI incidence, no HIV infections were observed among gbMSM using PrEP, demonstrating that PrEP is meeting a harm-reduction need.
- The impact of chemsex on STI incidence is stronger among gbMSM reporting polysubstance use and those reporting specific chemsex substances
- Age, education, and income are potentially modifying the effect of chemsex on STI incidence.

Abstract

Objectives: Use of illicit substances during sex (chemsex) among gay, bisexual and other men who have sex with men (gbMSM) may increase transmission of HIV and other sexually transmitted infections (STIs). Pre-exposure prophylaxis (PrEP) is highly effective at preventing HIV transmission, providing an important prevention tool for those who practice chemsex. However, it does not prevent acquisition of other STIs. We aim to examine the impact of chemsex on STI incidence among gbMSM and transgender women using PrEP in Montréal, Canada.

Methods: We linked baseline sociodemographic and behavioural data with follow-up STI testing from 2013-2020 among PrEP users in the l'Actuel PrEP Cohort. Focusing on the 24 months following PrEP initiation, we estimated the effect of chemsex reported at baseline on cumulative incidence of gonorrhea and chlamydia using Kaplan-Meier curves and survival analyses. We investigated the role of polysubstance use and effect modification by sociodemographic factors.

Results: There were 2,086 clients (2,079 cisgender gbMSM, 3 transgender gbMSM, 4 transgender women) who initiated PrEP, contributing 1,477 years of follow-up. There were no incident HIV infections among clients on PrEP. Controlling for sociodemographic confounders, clients reporting chemsex at baseline had a 32% higher hazard of gonorrhea/chlamydia diagnosis (adjusted HR=1.32; 95% CI: 1.10–1.57), equivalent to a risk increase of 8.9-percentage points (95% CI: 8.5–9.4) at 12 months. The effect was greater for clients who reported polysubstance use (adjusted HR=1.51; 95% CI: 1.21–1.89). The strength of the effect of chemsex on STI incidence varied by age, education, and income.

Conclusion: Among PrEP users, chemsex at baseline was linked to increased incidence of gonorrhea and chlamydia. This effect was stronger for people reporting multiple chemsex substances. The high STI incidence among gbMSM who report chemsex highlights the importance of PrEP for this population and the need for integrated services that address the complexities of sexualized substance use.

Keywords

Sexualized substance used; polysubstance use; HIV/AIDS; Neisseria gonorrhea; Chlamydia trachomatis; hepatitis C virus; sexually transmitted infections; gay, bisexual, and other men who have sex with men; pre-exposure prophylaxis; Canada.

1. Introduction

In the past two decades, the incidence of sexually transmitted infections (STI) has risen globally, and gay, bisexual and other men who have sex with men (gbMSM) continue to bear a disproportionate burden of disease.[1] In Canada, incidence rates for gonorrhea and chlamydia have steadily risen since the 1990s, growing faster for men than women between 2008 and 2017.[2] Rising STI incidence among gbMSM represents a public health priority due to the link between STIs and increased HIV-acquisition risk and the threat of antibiotic resistant STIs undermining available treatment options.[3,4]

In recent years, there has been increased attention towards the role of chemsex and pre-exposure prophylaxis (PrEP) in STI transmission among gbMSM. Chemsex is a form of sexualized drug use and is defined as the intentional use of illicit substances during sex to enhance pleasure. While the definition varies, these substances often include gamma-hydroxybutyrate (GHB), mephedrone and crystal meth.[5,6] Men often report increased pleasure, intimacy, and a heightened sense of confidence as motivations for chemsex.[7,8] Within the context of STI transmission, chemsex has been associated with condomless anal sex and increased number of partners –behaviours associated with increased acquisition and transmission of HIV and other STIs.[9–12] It has also been associated with higher prevalence of self-reported and diagnosed STIs.[13–15] Due to the demonstrated HIV acquisition risk associated with chemsex, recent methamphetamine use was included in the *HIV Incidence Risk Index for MSM* (HIRI-MSM) screening index for PrEP and chemsex was included as an eligibility criteria for PrEP in Québec's provincial guidelines.[16,17]

PrEP is a highly effective biomedical HIV-prevention method for populations at ongoing HIV acquisition risk. Oral PrEP taken daily or intermittently (event-driven regimen) has been partially reimbursable with public funds in Québec since 2013 and was approved by Health Canada in 2016.[16,18–20] Since PrEP prevents HIV acquisition, but not other STIs, concerns have been raised about potential increases in STI incidence following PrEP initiation.[21–23] However, these increases cannot be directly attributed to changes in behaviour, as higher STI incidence among PrEP users may be due to secular trends and regular STI screening during PrEP follow-up.[24,25] Some researchers have also highlighted that PrEP offers an opportunity to develop comprehensive HIV prevention programs that address STIs via regular screening and treatment.[3] Such programs

could include or link to services for chemsex and other forms of substance use, given that few interventions are available for gbMSM who practice chemsex.[26–28]

This study aims to examine the effect of chemsex on gonorrhea and chlamydia incidence among gbMSM and transgender women using PrEP. Leveraging seven years of longitudinal data from the *l'Actuel PrEP Cohort* (2013–2020) in Montréal (Canada) we (1) estimated the impact of chemsex at baseline on STI incidence in the first two years following PrEP initiation and (2) investigated whether this effect varies by number and type of chemsex substances reported and if selected sociodemographic characteristics are effect modifiers.

2. Methods

Study setting

Clinique médicale l'Actuel (l'Actuel) is a large sexual health clinic in Montréal that serves a population consisting mostly of gbMSM. L'Actuel specializes in STI/HIV prevention and care, and has been offering daily PrEP since January 2011 and intermittent PrEP since March 2015. (The clinic started offering PrEP based on trial results and interim guidelines published in the USA.)

The clinic established the *l'Actuel PrEP Cohort* in 2013 to measure the effectiveness of PrEP as an HIV prevention strategy and as a platform for future HIV prevention research. A detailed description of this cohort and study protocols can be found elsewhere.[29–31] Briefly, clients interested in PrEP have a baseline consultation with a nurse and a doctor to discuss PrEP needs and assess eligibility. During the consultation, clients complete a questionnaire on their sociodemographic profile, sexual health, and substance use. Clients who receive a PrEP prescription have a first follow-up visit after one month and regular quarterly follow-ups thereafter. Follow-up visits consist of renewal of the prescription, STI screening, and a questionnaire on PrEP adherence, side effects, and sexual behaviours. Clients may also use the clinic's STI testing services outside of their scheduled follow-up PrEP visits (e.g., if they experience symptoms or are notified by a partner).

Study population

This study includes all adult (≥18 years of age) gbMSM and transgender women who provided written informed consent, were seronegative for HIV at baseline, consulted for PrEP at l'Actuel between January 1, 2013 and May 31, 2020, and came to at least one follow-up visit

within the 180 days following their initial consultation. We defined gbMSM as cisgender or transgender men who either (a) identified as homosexual, bisexual, or another sexuality which would include attraction to men (e.g., pansexual, queer) or (b) reported having sex with a man in the past 12 months (P12M). All clients who self-identified as transgender women were included. Transgender women were included in the study because their sexual practices may be comparable to those of gbMSM if they are eligible for PrEP.

The database includes follow-up visits up to June 30, 2020. Follow-up consultations were lagged by one month to allow for sufficient time for the first PrEP follow-up for those consulting up to May 31, 2020. Given that a small proportion of clients had multiple baseline consultations – due to not initiating PrEP or after a prolonged discontinuation– we restricted the database to a client's first baseline consultation that led to PrEP initiation.

Exposure and outcome definitions

Chemsex was defined as reporting sexual relations under the effect of cocaine, ecstasy, GHB, crystal meth, ketamine, or crack at least once in the P12M at baseline. Other substances reported (i.e., alcohol, cannabis, poppers, opioids, and heroin) were not classified as chemsex. This definition is consistent with previous studies in Montréal and elsewhere.[5,8,32] We defined polysubstance use as reporting two or more chemsex substances, similarly to previous studies,[33–35] with the caveat that the questionnaire did not ask if substances were taken together.

For gonorrhea and chlamydia incidence and prevalence, we defined an STI diagnosis as a positive nucleic acid amplification test (NAAT) for anal and oral swabs, or urine samples. For seroprevalence of hepatitis C virus (HCV) infection, we defined prior history of infection as a positive antibody test. We defined incident HCV infections as first HCV-antibody positive test (seroconversion).

Statistical analyses

Sociodemographic characteristics, sexual behaviour, and past STI history are presented as they were asked in the questionnaire,[29] except for condom use in P12M, which was categorized. For prevalence of gonorrhea and chlamydia, and HCV seroprevalence at baseline, we linked data for tests performed at baseline or up to two months prior.

We conducted survival analysis to estimate the impact of chemsex at baseline on cumulative incidence of gonorrhea and chlamydia, focusing on the two years following PrEP

initiation. We linked baseline sociodemographic characteristics with follow-up visits and all gonorrhea and chlamydia tests performed after PrEP initiation. Follow-up started at the initial PrEP consultation and clients were censored at (1) their last follow-up visit, (2) the last visit prior to a temporary PrEP discontinuation (defined as a gap in follow-up of >180 days) or (3) after two years of follow-up. We considered three event dates: date of first diagnosis for either gonorrhea or chlamydia (primary outcome), date of first gonorrhea diagnosis, and date of first chlamydia diagnosis (all outcomes at any site). Additional sensitivity analyses stratified each STI by sample type.

Kaplan-Meier (KM) curves were used to compare cumulative STI incidence between the chemsex and the no-chemsex groups. We used Cox proportional hazards regression to examine the effect of chemsex at baseline on time to first STI diagnosis. We fit univariate models and multivariable models adjusted for age, education, income, PrEP regimen at baseline and year of entry into the cohort. We addressed missing data for education and income using multiple imputations, and pooled estimates from 12 imputations using Rubin's rules.[36,37] The proportional hazards assumption was verified by plotting the log cumulative hazard for both groups.[38] The absolute risk difference in STI diagnosis at 12 months was estimated as recommended by Austin[39] and confidence intervals were computed using a multiple imputation-Bootstrap procedure.[40] (Supplementary material presents details on imputation procedure and risk difference estimation.)

We also investigated the role of polysubstance use and specific substances. For polysubstance use, we estimated KM curves and fit a regression model using the chemsex variable trichotomized in mutually exclusive categories: no chemsex (reference), chemsex with only one substance, and polysubstance use. We performed a similar analysis for each substance, in which chemsex was stratified into clients who reported one specific substance, those who reported any of the other five, and those not reporting any chemsex.

To investigate effect modification, we fit regression models with product terms between chemsex and either age, income, or education.[41] To avoid small sample sizes, age and income were regrouped into three categories each and education was dichotomized (post-secondary vs not).

All analyses were performed with R 3.6.2.[42] Survival analysis was performed using the packages *survival* and *survminer*.[43,44] Multiple imputation was performed using the *mice* package.[45]

3. Results

Of 3,394 clients who consulted for PrEP at l'Actuel between January 2013 and May 2020, 382 (11%) were excluded because consent was not provided, 1 because the client was minor (<1%), 2 because they tested positive for HIV at baseline (<1%), and 86 because the clients were not gbMSM or transgender women (3%), leaving 2,923 clients who consulted for PrEP. Out of these clients, 677 did not return for any follow-up visits (20%) and 160 did not initiate PrEP within 180 days of their baseline consultation (5%), leaving 2,086 clients in the analytical sample (Supplementary Figure 1).

Of 2,086 clients with at least one follow-up visit, 2,079 were cisgender gbMSM, 3 were transgender gbMSM, and 4 were transgender women. One in four PrEP users (24%) reported chemsex at baseline. Participants contributed a total of 1,477 person-years of follow-up, and the median follow-up time was similar between groups: 6.5 months in the chemsex group vs 5.8 months in the no-chemsex group (Table 1).

Compared to clients who did not report chemsex, PrEP users who reported chemsex (P12M) at baseline were more likely to have consulted for PrEP in earlier years, and reported more occasional partners (median = 15 vs median = 10 in P12M), lower levels of condom use, and a higher proportion of previous post-exposure prophylaxis use (38% vs 32%) (Table 1). A more detailed description of all clients who consulted for PrEP has been reported elsewhere.[31]

Chemsex is associated with higher baseline proportion of self-reported STI history and prevalent STI diagnosis

At baseline, the chemsex group had a higher proportion of self-reported history of infection with gonorrhea (57% vs 39%), chlamydia (49% vs 31%), and syphilis (23% vs 15%) as compared to clients that did not report chemsex. Baseline STI prevalence was also higher in the chemsex group. Clients who reported chemsex at baseline had a higher prevalence of active gonorrhea and chlamydia infection compared to the no-chemsex group (15% vs 9% and 9% vs 7%, respectively). Two clients with positive HCV antibody tests at baseline had not reported prior history of HCV infection, one in each group (Table 1). One HCV seroconversion occurred during the study period

(in the chemsex group), corresponding to a cumulative incidence proportion of 0.2% (1/432) over two years.

Chemsex at baseline leads to higher incidence of gonorrhea and chlamydia

Median time to first diagnosis of either gonorrhea or chlamydia was shorter (10.7 months; 95% CI: 9.4–14.0) in the chemsex group compared to the no-chemsex group (16.4 months; 95% CI: 15.1–18.3) (Figure 1A). This translated to a crude hazard ratio of 1.40 (95% CI: 1.18–1.67). The impact of chemsex on STI incidence remained after controlling for sociodemographic confounders: the adjusted HR for the effect of chemsex on STI incidence was 1.32 (95% CI: 1.10–1.57) for either STI (Table 2; see also Supplementary Table 1). This is equivalent to a marginal risk increase of 8.9-percentage points (95% CI: 8.5–9.4) 12 months after PrEP initiation.

In STI-specific analyses, there was a clear separation of the cumulative incidence curve for the chemsex group for gonorrhea but not chlamydia (Figures 1B–C). The adjusted HRs for the effect of chemsex on STI incidence were 1.59 (95% CI: 1.28–1.97) for gonorrhea and 1.07 (95% CI: 0.84–1.36) for chlamydia (Table 2). The magnitude of the impact of chemsex on gonorrhea incidence was similar regardless of whether the infection was at any site, the rectum or throat, or the urethra. In contrast, the adjusted HR for chlamydia was 1.21 (95% CI: 0.93–1.57) for rectal and throat infections, and 0.98 (95% CI: 0.64–1.50) for urethral infections (Supplementary Table 2).

Polysubstance use and certain substances have a stronger effect on STI incidence

When chemsex was stratified according to polysubstance use, the cumulative incidence curve for the chemsex group (1 substance) was closer to that of the no-chemsex group. The median time to first STI diagnosis was 9.4 months (95% CI: 7.0–12.1) in the polysubstance use group, 14.6 months (95% CI: 10.5–23.4) in the chemsex group (1 substance) and 16.4 months (95% CI 15.1–18.3) in the no-chemsex group (Figure 1D). Compared with no indication of chemsex at baseline, the adjusted HR for chemsex (1 substance) was 1.12 (95% CI: 0.87–1.43) and 1.51 (95% CI: 1.21–1.89) for polysubstance use (Table 2).

In our analyses considering each chemsex substance separately, GHB, crystal meth, and crack were associated with a shorter median time to first STI diagnosis. In contrast, stratifying chemsex by cocaine or ecstasy did not substantially change the median time (Supplementary Figure 2).

Age, education, and income are effect-modifiers of the chemsex-STI relationship

When including a product term between age and chemsex, the effect of chemsex at baseline on STI incidence varied by age: the HR was 1.71 (95% CI: 1.36–2.15) among PrEP users aged 18–35, 0.77 (95% CI: 0.55–1.07) among those aged 36-50 and 1.53 (95% CI: 0.90–2.60) among those >50 years old. When the interaction term was between education and chemsex, the effect of chemsex was greater among clients with secondary education or less (HR of 1.61; 95% CI: 0.98-2.64) than among clients with post-secondary education (HR of 1.27; 95% CI: 1.04–1.55). For income, the magnitude of the effect of chemsex decreased among clients reporting higher incomes: the HR was 1.71 (95% CI: 1.23-2.36) for clients reporting income of $35,000 CAD or less, 1.25 (95% CI: 0.96–1.63) for clients reporting $35,001-75,000 and 1.05 (95% CI: 0.72–1.54) for clients reporting income of over $75,000 (Table 3).

Table 1: Sociodemographic characteristics, sexual behaviours, sexually transmitted infection (STI) history and prevalent STIs for pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013–2020).

	Reported chemsex		No chemsex reported		Total	
Total	507		1,579		2,086	
Median follow-up time (months)	6.5		5.8		5.9	
Total follow-up time (person-years)	370		1,170		1,477	
Age (median, IQR)	33	(28–43)	36	(29–46)	36	(29–45)
Gender identity (n,%)						
Cis men	503	99.2%	1,576	99.8%	2,079	99.7%
Trans men	1	0.2%	2	0.1%	3	0.1%
Trans women	3	0.6%	1	0.1%	4	0.2%
Sexual orientation (n,%)						
Homosexual	483	95.3%	1,482	93.9%	1,965	94.2%
Bisexual	21	4.1%	92	5.8%	113	5.4%
Heterosexual	2	0.4%	3	0.2%	5	0.2%
Other	0	0.0%	1	0.1%	1	<0.1%
Missing	*1*	*0.2%*	*1*	*0.1%*	*2*	*0.1%*
Education (n,%)						
Primary	5	1.0%	9	0.6%	14	0.7%
Secondary	70	13.8%	145	9.2%	215	10.3%
CEGEP	113	22.3%	203	12.9%	316	15.2%
University	255	50.3%	800	50.7%	1055	50.6%
Missing	*64*	*12.6%*	*422*	*26.7%*	*486*	*23.3%*
Annual income ($) (n,%)						
≤10,000	30	5.9%	89	5.6%	119	5.7%
10,001–20,000	47	9.3%	115	7.3%	162	7.8%

20,001–35,000	73	14.4%	141	8.9%	214	10.3%
35,001–55,000	120	23.7%	298	18.9%	418	20.0%
55,001–75,000	96	18.9%	231	14.6%	327	15.7%
>75,000	100	19.7%	368	23.3%	468	22.4%
Missing	*41*	*8.1%*	*337*	*21.3%*	*378*	*18.1%*
Intravenous drug use in P12M (n,%)						
Yes	5	1.0%	7	0.4%	12	0.6%
Missing	*131*	*25.8%*	*539*	*34.1%*	*670*	*32.1%*
Year of baseline consultation (n,%)						
2013	8	1.6%	16	1.0%	24	1.2%
2014	29	5.7%	49	3.1%	78	3.7%
2015	119	23.5%	254	16.1%	373	17.9%
2016	146	28.8%	332	21.0%	478	22.9%
2017	102	20.1%	311	19.7%	413	19.8%
2018	69	13.6%	307	19.4%	376	18.0%
2019	28	5.5%	250	15.8%	278	13.3%
2020	6	1.2%	60	3.8%	66	3.2%
Number of regular partners in P12M						
Median (IQR)	2	(1–3)	2	(1–3)	2	(1–3)
Missing (n,%)	*78*	*15.4%*	*422*	*26.7%*	*500*	*24.0%*
Number of occasional partners in P12M						
Median (IQR)	15	(6–30)	10	(5–20)	10	(5–20)
Missing (n,%)	*57*	*11.2%*	*403*	*25.5%*	*460*	*22.1%*
Condom use in P12M (insertive anal sex) (n,%)**						
0–25%	90	21.0%	162	13.8%	252	15.7%
>25–50%	75	17.5%	143	12.2%	218	13.6%
>50–75%	47	11.0%	80	6.8%	127	7.9%
>75–100%	176	41.0%	594	50.6%	770	48.1%
Missing	*41*	*9.6%*	*194*	*16.5%*	*235*	*14.7%*
Condom use in P12M (receptive anal sex) (n,%)**						
0–25%	64	15.3%	97	9.1%	161	10.8%
>25–50%	43	10.3%	86	8.1%	129	8.7%
>50–75%	37	8.8%	55	5.2%	92	6.2%
>75–100%	121	28.9%	459	43.1%	580	39.1%
Missing	*154*	*36.8%*	*368*	*34.6%*	*522*	*35.2%*
Previous PEP use (n,%)						
Yes	193	38.1%	497	31.5%	690	33.1%
Missing	*26*	*5.1%*	*285*	*18.0%*	*311*	*14.9%*
Self-reported STI history, ever (n,%)						
Gonorrhea	291	57.4%	617	39.1%	908	43.5%
Chlamydia	249	49.1%	486	30.8%	735	35.2%
Syphilis	117	23.1%	240	15.2%	357	17.1%
Hepatitis C virus	6	1.2%	10	0.6%	16	0.8%
Missing	*17*	*3.4%*	*170*	*10.8%*	*187*	*9.0%*
Prevalent STI diagnoses – PCR (n,%)						
Gonorrhea	78	15.4%	140	8.9%	218	10.5%

Chlamydia	44	8.7%	116	7.3%	160	7.7%
Missing	*36*	*7.1%*	*141*	*8.9%*	*177*	*8.5%*
Seroprevalence (n,%)						
Hepatitis C virus	2	0.4%	2	0.1%	4	0.2%
Missing	*73*	*14.4%*	*310*	*19.6%*	*383*	*18.4%*

CEGEP: *Collège d'enseignement général et professionnel*, Québec's system of post-secondary education which offers pre-university and professional degrees; IQR: inter-quartile range; P12M: past 12 months; PEP: post-exposure prophylaxis; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.

** for condom use variables, the denominator was only clients who reported either insertive or receptive anal sex, hence the numbers here may not add up to the total in the first row

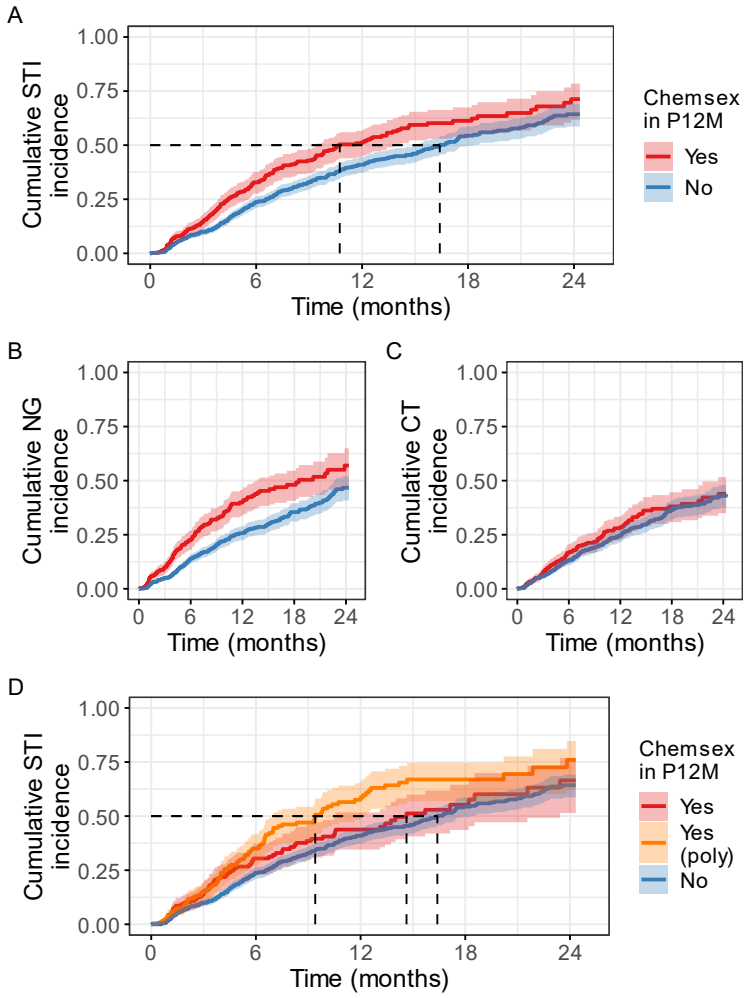


Figure 1: Cumulative sexually transmitted infection (STI) incidence among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013–2020). A) Gonorrhea or chlamydia, any site. B) Gonorrhea, any site. C) Chlamydia, any site. D) Gonorrhea or chlamydia, any site, chemsex stratified by polysubstance use (≥2 chemsex substances) or not (1 substance). 95% confidence intervals are shown as a shaded region, dotted lines show median time to first diagnosis. CT: *Chlamydia trachomatis*; NG: *Neisseria gonorrhea*; PrEP: pre-exposure prophylaxis; P12M: past 12 months; STI: sexually transmitted infection.

Table 2: Effect of chemsex at baseline on time to first sexually transmitted infection (STI) diagnosis among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013–2020).

		Crude model		Adjusted model	
Outcome	**# of events**	**HR**	**95% CI**	**HR**	**95% CI**
Model with chemsex only					
Gonorrhea or chlamydia	614	1.40	(1.18 – 1.67)	1.32	(1.10 – 1.57)
Gonorrhea	410	1.70	(1.38 – 2.08)	1.59	(1.28 – 1.97)
Chlamydia	369	1.15	(0.92 – 1.45)	1.07	(0.84 – 1.36)
Model with chemsex and polysubstance use					
Gonorrhea or chlamydia	614				
No chemsex		REF	–	–	–
Chemsex		1.20	(0.94 – 1.53)	1.12	(0.87 – 1.43)
Polysubstance use		1.61	(1.30 – 1.99)	1.51	(1.21 – 1.89)

Models adjusted for age, education, income, PrEP regimen at baseline and year of entry into the cohort (all categorical). CI: confidence interval; HR: hazard ratio.

Table 3: Modification of the effect of chemsex at baseline on time to first sexually transmitted infection (STI) diagnosis among pre-exposure prophylaxis (PrEP) users by age, education, or income.

	No chemsex reported		Chemsex reported		HR (95% CI) for chemsex within strata
	n	**HR (95% CI)**	***n***	**HR (95% CI)**	
Effect modification by age					
18–35	750	1.57 (1.17 – 2.10)	290	2.69 (1.96 – 3.68)	1.71 (1.36 – 2.15)
36–50	575	1.30 (0.97 – 1.74)	164	1.00 (0.67 – 1.48)	0.77 (0.55 – 1.07)
>50	254	1.00	53	1.53 (0.90 – 2.60)	1.53 (0.90 – 2.60)
Effect modification by education					
Secondary or less	230	1.00	87	1.61 (0.98 – 2.64)	1.61 (0.98 – 2.64)
Post-secondary	1,349	1.16 (0.81 – 1.65)	420	1.47 (1.03 – 2.11)	1.27 (1.04 – 1.55)
Effect modification by income ($CAD)					
≤35,000	449	1.00	162	1.71 (1.23 – 2.36)	1.71 (1.23 – 2.36)
35,001–75,000	668	1.01 (0.76 – 1.34)	238	1.26 (0.92 – 1.71)	1.25 (0.96 – 1.63)
>75,000	462	1.18 (0.88 – 1.57)	107	1.24 (0.82 – 1.86)	1.05 (0.72 – 1.54)

Models adjusted for age, education, income, PrEP regimen at baseline and year of entry into the cohort (all categorical). CI: confidence interval; HR: hazard ratio.
For education and income, the group size *n* in each cell is the average group size from the imputed datasets.

4. Discussion

The prevalence of chemsex among gbMSM using PrEP and the high STI incidence in this population highlight unmet prevention needs arising from the substance use and STI syndemic.[46,47] In this study, we found that participants using PrEP were 32% (95% CI: 10–57%) more likely to be diagnosed with gonorrhea or chlamydia if they reported chemsex at

baseline, relative to those who did not report chemsex. This was equivalent to an absolute risk increase of 8.9-percentage points (95% CI: 8.5–9.4) one year after PrEP initiation. This effect was heterogeneous, however, and we found that reporting polysubstance use had a stronger effect on STI incidence. Despite the high STI incidence, there were no incident HIV infections in this cohort, demonstrating how PrEP is meeting a harm reduction need for gbMSM, including those who practice chemsex.

Using baseline data, we observed a higher prevalence of gonorrhea (15% vs 9%) and chlamydia (9% vs 7%) infection among PrEP users who reported chemsex at the initial consultation. These results are consistent with previous cross-sectional studies that showed an association with self-reported and lab-confirmed STI diagnosis among gbMSM.[11,14,15] In our longitudinal analyses, chemsex at baseline led to higher cumulative incidence of gonorrhea and chlamydia. Analyses stratified by infection site showed that chemsex at baseline was strongly linked with gonorrhea incidence regardless of the site of infection. In contrast, there was an effect of chemsex on chlamydia infection at the rectum or throat but not on urethral infection. The stronger impact of chemsex on gonorrhea incidence and the difference for chlamydia by infection site could be due to difference in transmission efficiencies. For example, gonorrhea transmission may occur from the throat to the urethra or rectum during oral sex or anal play, but these transmission routes are less likely for chlamydia.[48,49]

People who engage in chemsex may use different substances and not all of them may have the same impact on STI acquisition risk. In our study, we found that crystal meth and GHB –more commonly associated with chemsex culture– were associated with shorter median time to STI diagnosis than other chemsex substances. In contrast, cocaine and ecstasy –which did not show this trend– have more diverse uses among gbMSM.[5,6,50] Thus, reporting sex while under the influence of cocaine or ecstasy may reflect a combination of chemsex and substance use prior to a sexual encounter (e.g., while at a bar or club). A previous study in Montréal found that sexualized substance use with crystal meth or GHB had stronger association with condomless anal sex (with a seropositive partner or of unknown serostatus) than cocaine or ecstasy.[9] In contrast, a study in the Netherlands found similar magnitude of effect for GHB, ecstasy and cocaine, a difference that could be attributed to the smaller sampler size, cross-sectional design and different patterns of substance use in this country.[34] Additionally, some authors have argued that –due to the stronger effects and less documented history of use of crystal meth and GHB– sexualized use of these

substances may be linked to higher risk of harm.[5,28] Taken together, this evidence highlights the importance of considering the complexities of chemsex when developing harm reduction interventions.

We also observed possible modification of the effect of chemsex on STI incidence by age, education and income, which may point to greater service needs within specific subpopulations. Qualitative evidence suggests that some gbMSM incorporate strategies for harm reduction in their chemsex practices, such as strict condom use, open discussion of HIV serostatus, and having established plans to address overdoses or loss of consciousness.[10,51] It is possible that the stronger effect of chemsex among gbMSM aged 18-35 and >50 years is due to age-dependant differences in the presence of such strategies and to different substance use patterns. Similarly, the weakening of the chemsex effect on STI incidence for higher levels of income and post-secondary education may be due to income-related differences in access to chemsex substances and sexual mixing patterns. This is in line with syndemic theory as applied to STIs and substance use among gbMSM,[46] which argues that health disparities are rooted in structural conditions such as social and economic marginalization (reflected by lower access to education, revenue, and prevention strategies).

Our results should be interpreted considering several limitations. First, despite adjusting for sociodemographic confounders, the chemsex-STI relationship could remain confounded by unmeasured factors. Second, the dynamic nature of PrEP use means that discontinuation is common, reducing sample size. However, this type of attrition was not differential between groups. Third, there were no questions on frequency of chemsex and this exposure was only measured at the initial consultation. To alleviate this shortcoming we restricted our follow-up to the first two years, since there is evidence of little within-person change in chemsex practices over this timeframe.[52] Fourth, it is possible some clients who practiced chemsex did not report it due to perceived stigma. This exposure misclassification would be non-differential with respect to STI outcome ascertainment, leading to a bias towards the null. Lastly, there were not enough transgender women in the study to perform stratified analyses for these individuals who might have different STI acquisition risks.

The strengths of our study include the use of prospectively collected, longitudinal clinical data spanning over seven years of follow-up from a large cohort, enabling more granular analyses of chemsex and exploratory effect modification analyses. The STI data came from lab-confirmed

diagnoses and was prospectively collected through regular screening, an important characteristic given that many STIs are asymptomatic.

5. Conclusions

Among gbMSM using PrEP, chemsex and polysubstance use led to increased incidence of gonorrhea and chlamydia. The lack of incident HIV diagnoses among PrEP users suggests that PrEP is meeting a prevention need among people who practice chemsex. However, the prevalence of chemsex and high STI incidence in this population highlight the need for integrated services that address the intersection of sexualized substance use and sexual health. Future work should examine the role of specific substances and potential effect modification by age, education, and income to tailor services to subpopulations with the greatest unmet prevention needs.

6. References

1 Chow EPF, Grulich AE, Fairley CK. Epidemiology and prevention of sexually transmitted infections in men who have sex with men at risk of HIV. *Lancet HIV* 2019;**6**:e396–405. doi:10.1016/S2352-3018(19)30043-8

2 Public Health Agency of Canada. Report on sexually transmitted infections in Canada, 2017. Public Health Agency of Canada 2019. https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-sexually-transmitted-infections-canada-2017.html (accessed 13 Feb 2020).

3 Scott HM, Klausner JD. Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US. *AIDS Res Ther* 2016;**13**:5. doi:10.1186/s12981-016-0089-8

4 Unemo M, Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and Mycoplasma genitalium. *Nat Rev Urol* 2017;**14**:139–52. doi:10.1038/nrurol.2016.268

5 Bourne A, Reid D, Hickson F, *et al.* The Chemsex study: drug use in sexual settings among gay and bisexual men in Lambeth, Southwark and Lewisham. London: : Sigma Research, London School of Hygiene & Tropical Medicine 2014. https://researchonline.lshtm.ac.uk/id/eprint/2197245 (accessed 13 Jul 2020).

6 Stuart D. Chemsex: origins of the word, a history of the phenomenon and a respect to the culture. *Drugs Alcohol Today* 2019;**19**:3–10. doi:10.1108/DAT-10-2018-0058

7 Flores-Aranda J, Goyette M, Aubut V, *et al.* Let's talk about chemsex and pleasure: the missing link in chemsex services. *Drugs Alcohol Today* 2019;**19**:189–96. doi:10.1108/DAT-10-2018-0045

8 Maxwell S, Shahmanesh M, Gafos M. Chemsex behaviours among men who have sex with men: A systematic review of the literature. *Int J Drug Policy* 2019;**63**:74–89. doi:10.1016/j.drugpo.2018.11.014

9 Blais M, Otis J, Lambert G, *et al.* Consommation de substances en contexte sexuel chez des hommes gbHSH de Montréal : 2009-2016. *Drogues, santé et société* 2018;**17**:76. doi:10.7202/1062117ar

10 Bourne A, Reid D, Hickson F, *et al.* Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: findings from a qualitative study. *Sex Transm Infect* 2015;**91**:564–8. doi:10.1136/sextrans-2015-052052

11 Curtis TJ, Rodger AJ, Burns F, *et al.* Patterns of sexualised recreational drug use and its association with risk behaviours and sexual health outcomes in men who have sex with men in London, UK: a comparison of cross-sectional studies conducted in 2013 and 2016. *Sex Transm Infect* 2020;**96**:197–203. doi:10.1136/sextrans-2019-054139

12 Hammoud MA, Vaccher S, Jin F, *et al.* The new MTV generation: Using methamphetamine, Truvada™, and Viagra™ to enhance sex and stay safe. *Int J Drug Policy* 2018;**55**:197–204. doi:10.1016/j.drugpo.2018.02.021

13 Guerra FM, Salway TJ, Beckett R, *et al.* Review of sexualized drug use associated with sexually transmitted and blood-borne infections in gay, bisexual and other men who have sex with men. *Drug Alcohol Depend* 2020;**216**:108237. doi:10.1016/j.drugalcdep.2020.108237

14 Ottaway Z, Finnerty F, Amlani A, *et al.* Men who have sex with men diagnosed with a sexually transmitted infection are significantly more likely to engage in sexualised drug use. *Int J STD AIDS* 2017;**28**:91–3. doi:10.1177/0956462416666753

15 Pufall EL, Kall M, Shahmanesh M, *et al.* Sexualized drug use ('chemsex') and high-risk sexual behaviours in HIV-positive men who have sex with men. *HIV Med* 2018;**19**:261–70. doi:10.1111/hiv.12574
16 Direction générale de la santé publique. La prophylaxie préexposition au virus de l'immunodéficience humaine : Guide pour les professionnels de la santé du Québec. Ministère de la Santé et des Services sociaux 2019. https://publications.msss.gouv.qc.ca/msss/document-000313/ (accessed 21 Aug 2020).
17 Smith DK, Pals SL, Herbst JH, *et al.* Development of a Clinical Screening Index Predictive of Incident HIV Infection Among Men Who Have Sex With Men in the United States. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 2012;**60**:421–7. doi:10.1097/QAI.0b013e318256b2f6
18 Direction générale de la santé publique. Avis intérimaire sur la prophylaxie préexposition au virus de l'immunodéficience humaine. Ministère de la Santé et des Services sociaux 2013. http://site.ebrary.com/id/10863343 (accessed 24 Mar 2021).
19 Health Canada. Regulatory Decision Summary - TRUVADA. 2016.https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00107 (accessed 20 Feb 2021).
20 Spinner CD, Boesecke C, Zink A, *et al.* HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. *Infection* 2016;**44**:151–8. doi:10.1007/s15010-015-0850-2
21 Nguyen V-K, Greenwald ZR, Trottier H, *et al.* Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. *AIDS* 2018;**32**:523–30. doi:10.1097/QAD.0000000000001718
22 Traeger MW, Cornelisse VJ, Asselin J, *et al.* Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection. *JAMA* 2019;**321**:1380. doi:10.1001/jama.2019.2947
23 Traeger MW, Schroeder SE, Wright EJ, *et al.* Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis. *Clin Infect Dis* 2018;**67**:676–86. doi:10.1093/cid/ciy182
24 Marcus JL, Katz KA, Krakower DS, *et al.* Risk Compensation and Clinical Decision Making — The Case of HIV Preexposure Prophylaxis. *N Engl J Med* 2019;**380**:510–2. doi:10.1056/NEJMp1810743
25 Marcus JL, Volk JE, Snowden JM. Concerns about a study on sexually transmitted infections after initiation of HIV preexposure prophylaxis. *AIDS* 2018;**32**:955–6. doi:10.1097/QAD.0000000000001769
26 Flores-Aranda J, Goyette M, Larose-Osterrath C. Online Intervention as Strategy to Reach Men Who Have Sex With Other Men and Who Use Substances in a Sexual Context. Development of the MONBUZZ.ca Project. *Front Psychiatry* 2019;**10**:183. doi:10.3389/fpsyt.2019.00183
27 Stardust Z, Kolstee J, Joksic S, *et al.* A community-led, harm-reduction approach to chemsex: case study from Australia's largest gay city. *Sex Health* 2018;**15**:179. doi:10.1071/SH17145
28 Stuart D, Weymann J. ChemSex and care-planning: One year in practice. *HIV Nursing* 2015;**15**:24–8.

29 Greenwald ZR, Maheu-Giroux M, Szabo J, *et al.* Cohort profile: l'Actuel Pre-Exposure Prophylaxis (PrEP) Cohort study in Montreal, Canada. *BMJ Open* 2019;**9**. doi:10.1136/bmjopen-2018-028768
30 Xia Y, Greenwald ZR, Milwid RM, *et al.* Pre-exposure Prophylaxis Uptake Among Men Who Have Sex With Men Who Used nPEP: A Longitudinal Analysis of Attendees at a Large Sexual Health Clinic in Montréal (Canada). *J Acquir Immune Defic Syndr* 2020;**85**:408–15. doi:10.1097/QAI.0000000000002472
31 Flores Anato JL, Panagiotoglou D, Greenwald ZR, *et al.* Chemsex practices and pre-exposure prophylaxis (PrEP) trajectories among individuals consulting for PrEP at a large sexual health clinic in Montréal, Canada (2013-2020). *Drug Alcohol Depend* 2021;**226**:108875. doi:10.1016/j.drugalcdep.2021.108875
32 Messier-Peet M, Herak Apelian, Gilles Lambert, *et al.* Chemsex & Mental Health in gbMSM in Montreal: Results from Engage Cycle 1. 2018.https://www.engage-men.ca/our-work/orals/ (accessed 21 May 2020).
33 Daskalopoulou M, Rodger A, Phillips AN, *et al.* Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. *Lancet HIV* 2014;**1**:e22–31. doi:10.1016/S2352-3018(14)70001-3
34 Evers YJ, Liere GAFSV, Hoebe CJPA, *et al.* Chemsex among men who have sex with men living outside major cities and associations with sexually transmitted infections: A cross-sectional study in the Netherlands. *PLOS ONE* 2019;**14**:e0216732. doi:10.1371/journal.pone.0216732
35 Tomkins A, Ahmad S, Cannon L, *et al.* Prevalence of recreational drug use reported by men who have sex with men attending sexual health clinics in Manchester, UK. *Int J STD AIDS* 2018;**29**:350–6. doi:10.1177/0956462417725638
36 Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;**45**:1–67. doi:10.18637/jss.v045.i03
37 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;**30**:377–99. doi:10.1002/sim.4067
38 Moore DF. *Applied Survival Analysis Using R*. Springer International Publishing 2016. doi:10.1007/978-3-319-31245-3
39 Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol* 2010;**63**:46–55. doi:10.1016/j.jclinepi.2009.03.012
40 Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Statistics in Medicine* 2018;**37**:2252–66. doi:10.1002/sim.7654
41 Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol* 2012;**41**:514–20. doi:10.1093/ije/dyr218
42 R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: : R Foundation for Statistical Computing 2019. https://www.R-project.org/ (accessed 23 Dec 2020).
43 Kassambara A, Kosinski M, Biecek P, *et al. survminer: Drawing Survival Curves using "ggplot2."* 2019. https://CRAN.R-project.org/package=survminer (accessed 23 Dec 2020).
44 Therneau TM. *survival: A Package for Survival Analysis in R*. 2019. https://CRAN.R-project.org/package=survival (accessed 23 Dec 2020).

45 Buuren S van, Groothuis-Oudshoorn K, Vink G, *et al. mice: Multivariate Imputation by Chained Equations*. 2021. https://CRAN.R-project.org/package=mice (accessed 16 Jun 2021).
46 Halkitis PN, Wolitski RJ, Millett GA. A holistic approach to addressing HIV infection disparities in gay, bisexual, and other men who have sex with men. *Am Psychol* 2013;**68**:261–73. doi:10.1037/a0032746
47 Singer M, Bulled N, Ostrach B, *et al.* Syndemics and the biosocial conception of health. *Lancet* 2017;**389**:941–50. doi:10.1016/S0140-6736(17)30003-X
48 Barbee LA, Khosropour CM, Dombrowski JC, *et al.* An estimate of the proportion of symptomatic gonococcal, chlamydial and non-gonococcal non-chlamydial urethritis attributable to oral sex among men who have sex with men: a case–control study. *Sex Transm Infect* 2016;**92**:155–60. doi:10.1136/sextrans-2015-052214
49 Chow EPF, Fairley CK. The role of saliva in gonorrhoea and chlamydia transmission to extragenital sites among men who have sex with men: new insights into transmission. *J Int AIDS Soc* 2019;**22 Suppl 6**:e25354. doi:10.1002/jia2.25354
50 Hawkins BW, Armstrong HL, Kesselring S, *et al.* Substance Use as a Mechanism for Social Inclusion among Gay, Bisexual, and Other Men Who Have Sex with Men in Vancouver, Canada. *Subst Use Misuse* 2019;**54**:1945–55. doi:10.1080/10826084.2019.1621901
51 Santoro P, Rodríguez R, Morales P, *et al.* One "chemsex" or many? Types of chemsex sessions among gay and other men who have sex with men in Madrid, Spain: findings from a qualitative study. *Int J Drug Policy* 2020;**82**:102790. doi:10.1016/j.drugpo.2020.102790
52 Sewell J, Cambiano V, Speakman A, *et al.* Changes in chemsex and sexual behaviour over time, among a cohort of MSM in London and Brighton: Findings from the AURAH2 study. *Int J Drug Policy* 2019;**68**:54–61. doi:10.1016/j.drugpo.2019.03.021

Supplementary methods

Multiple imputation

Missing values for education (n = 486; 23%) and income (n = 378; 18%) were handled using multiple imputation by chained equations (MICE) [1]. To examine the fraction of missing information (FMI) in the regression models used, we ran a preliminary analysis with 5 imputations. The highest FMI value was estimated to be 0.18 and was estimated for one of the interaction terms in the regression models for effect modification (education*chemsex). We therefore chose to perform 12 imputations, in line with recommendations by White and colleagues [2].

The predictors used in the multiple imputation were the chemsex exposure (binary indicator), polysubstance use (binary indicator), event indicator for the primary outcome (STI diagnosis), cumulative hazard for the primary outcome (estimated using Nelson-Aalen estimator), and all confounders included in the regression models (age, education, income, PrEP regimen at baseline, and year of initial consult).

Education and income were imputed separately for the main analyses and for the reclassified versions used in effect modification analyses. Education was modelled using a polytomous or unordered logistic regression (main analyses) and logistic regression (effect modification analysis). Both income variables (the one used in the main analyses and the one used in effect modification analyses) were modelled using proportional odds regression.

Risk difference estimation

The risk difference in STI diagnosis at 12 months attributable to chemsex reported at baseline was estimated as recommended by Austin [3]. Confidence intervals were computed using a multiple imputation-Bootstrap procedure (n = 1,000) as recommended by Schomaker and Heumann [4].

For a single imputed dataset, we fit a Cox model as specified in the Methods section of the main text with chemsex at baseline as the main exposure. We used this model to predict the probability of survival for each individual, setting the time to 12 months and exposure to 1 ("chemsex"). We then determined the probability of the event, $1 - \Pr(survival)$, and the predicted absolute risk, defined as the mean of all predicted probabilities of an STI diagnosis. This procedure was repeated with exposure set to 0 ("no chemsex") to predict the absolute risk had everyone been unexposed. For each imputed dataset, this was repeated 1,000 times (resampling

from the predicted probabilities) to generate a Bootstrap distribution of the risk difference after 12 months, defined as $mean(\Pr(event|chemsex = 1)) - mean(\Pr(event|chemsex = 0))$.

The 12 Bootstrap distributions of size 1,000 were used to compute the within- and between-imputation variance of the risk difference estimates. These were then used to generate the 95% confidence intervals based on a *t*-distribution with 11 degrees of freedom.

References for "Supplementary Methods"

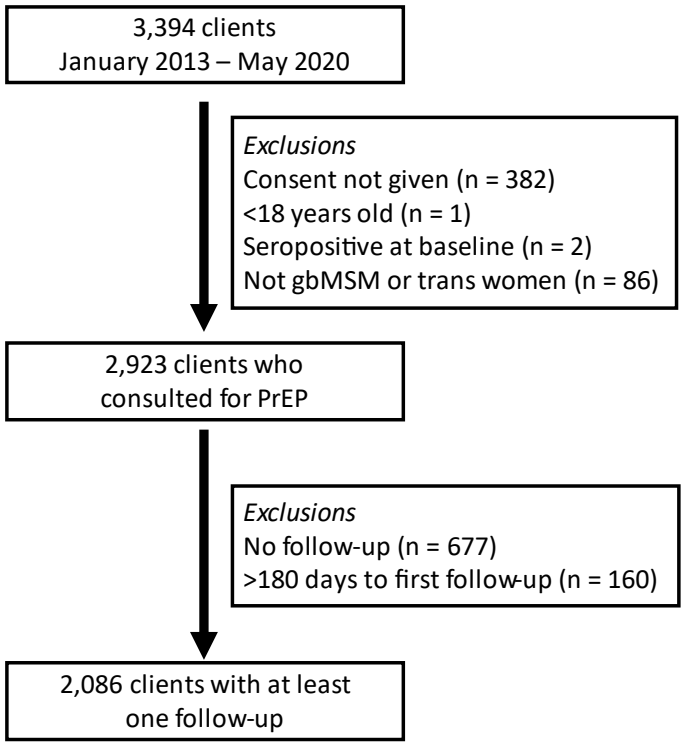
1 Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;**45**:1–67. doi:10.18637/jss.v045.i03

2 White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;**30**:377–99. doi:10.1002/sim.4067

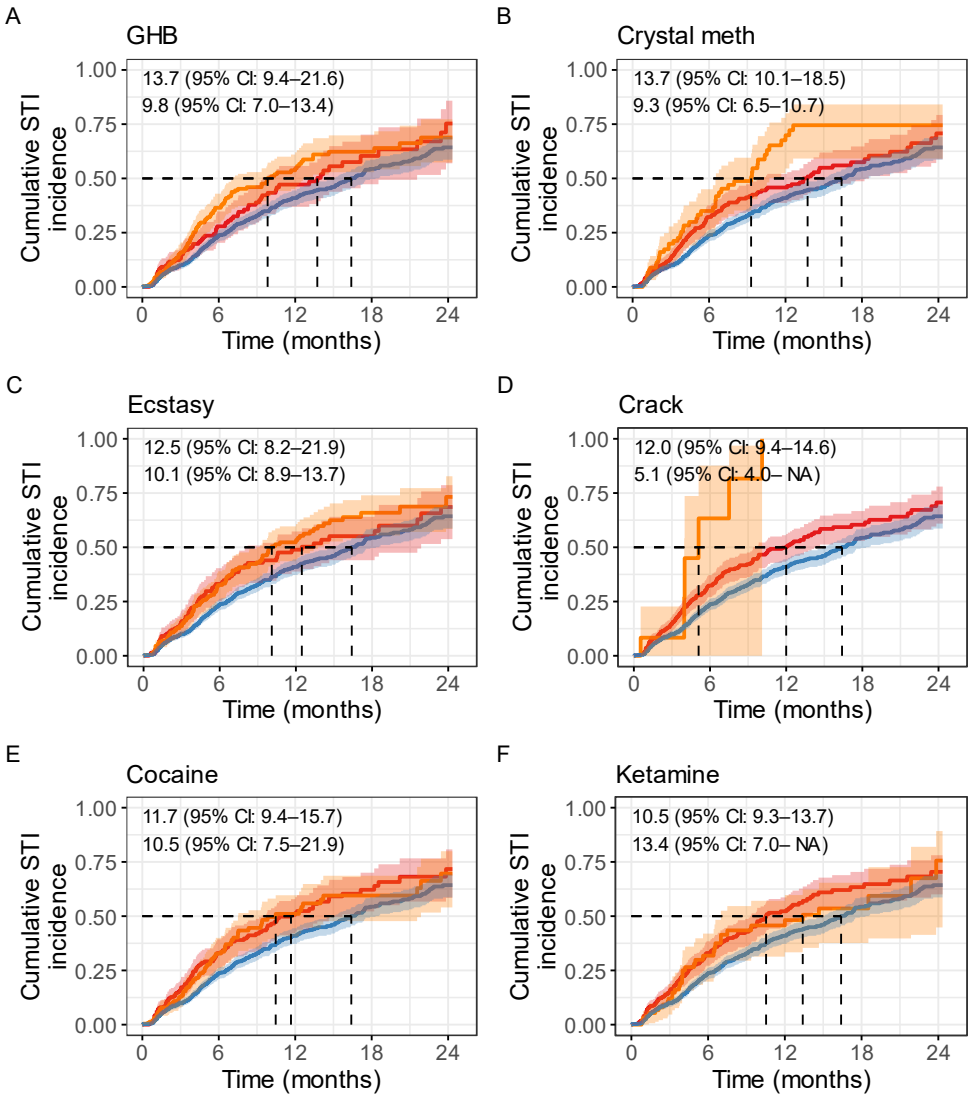
3 Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol* 2010;**63**:46–55. doi:10.1016/j.jclinepi.2009.03.012

4 Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. *Statistics in Medicine* 2018;**37**:2252–66. doi:10.1002/sim.7654

Supplementary results



Supplementary Figure 1: Flowchart of inclusion criteria of clients initiating pre-exposure prophylaxis (PrEP) at the Clinique médicale l'Actuel in Montréal, Canada. gbMSM: gay, bisexual and other men who have sex with men; PrEP: pre-exposure prophylaxis.



Supplementary Figure 2: Cumulative incidence of gonorrhea and chlamydia among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013–2020). For the six chemsex substances considered, the chemsex group was stratified into two sub-groups: individuals who reported chemsex including the substance (orange) and individuals who reported chemsex excluding the substance (red). The reference group is no chemsex reported (blue). 95% confidence intervals are shown as a shaded region, dotted lines show median time to first diagnosis. Median times to first STI diagnoses are shown in each panel, for the chemsex group excluding the substance (top) and for the individuals who reported the substance (bottom). GHB: gamma-hydroxybutyrate; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.

Supplementary Table 1: Hazard ratios for the main adjusted model of the effect of chemsex at baseline on time to first sexually transmitted infection (STI) diagnosis among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013–2020).

Term	HR	95% CI	Standard error	p-value
Chemsex	1.32	(1.10 – 1.57)	0.091	0.003
Age				
18–25	REF	–	–	–
26–30	0.79	(0.59 – 1.08)	0.155	0.138
31–35	0.81	(0.60 – 1.09)	0.151	0.164
36–40	0.68	(0.50 – 0.94)	0.163	0.021
41–45	0.53	(0.37 – 0.75)	0.177	<0.001
46–50	0.41	(0.28 – 0.61)	0.199	<0.001
>50	0.51	(0.36 – 0.71)	0.170	<0.001
Education level				
Secondary or under	REF	–	–	–
CEGEP	1.05	(0.77 – 1.45)	0.161	0.746
University	1.10	(0.84 – 1.44)	0.135	0.478
Income ($CAD)				
≤10,000	REF	–	–	–
10,001–20,000	0.85	(0.54 – 1.33)	0.228	0.47
20,001–35,000	0.96	(0.64 – 1.44)	0.203	0.849
35,001–55,000	0.89	(0.59 – 1.34)	0.207	0.562
55,001–75,000	0.85	(0.57 – 1.28)	0.205	0.444
>75,000	1.00	(0.67 – 1.47)	0.198	0.984
PrEP schedule				
Daily	REF	–	–	–
Intermittent	0.76	(0.59 – 0.96)	0.124	0.024
Year of entry into the cohort				
2013–2014	REF	–	–	–
2015	1.42	(0.97 – 2.08)	0.195	0.072
2016	1.17	(0.80 – 1.70)	0.192	0.413
2017	1.44	(0.98 – 2.10)	0.195	0.064
2018	0.91	(0.61 – 1.36)	0.205	0.649
2019–2020	0.89	(0.58 – 1.37)	0.220	0.587

CEGEP: *Collège d'enseignement général et professionnel*, Québec's system of post-secondary education which offers pre-university and professional degrees; CI: confidence interval; PrEP: pre-exposure prophylaxis.

Supplementary Table 2: Effect of chemsex at baseline on time to first sexually transmitted infection (STI) diagnosis among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013–2020), stratified by STI and site of infection.

		Crude models		Adjusted models	
Outcome	**# of events**	**HR**	**95% CI**	**HR**	**95% CI**
Gonorrhea or chlamydia (any site)	614	1.40	(1.18 – 1.67)	1.32	(1.10 – 1.57)
Gonorrhea					
Any site	410	1.70	(1.38 – 2.08)	1.59	(1.28 – 1.97)
Rectum or throat	377	1.78	(1.44 – 2.20)	1.63	(1.30 – 2.03)
Urethra	78	1.42	(0.88 – 2.29)	1.55	(0.93 – 2.57)
Chlamydia					
Any site	369	1.15	(0.92 – 1.45)	1.07	(0.84 – 1.36)
Rectum or throat	292	1.32	(1.03 – 1.70)	1.21	(0.93 – 1.57)
Urethra	121	1.01	(0.67 – 1.51)	0.98	(0.64 – 1.50)

Models adjusted for age, education, income, PrEP regimen at baseline and year of entry into the cohort (all categorical). CI: confidence interval; HR: hazard ratio.

Chapter 6

Discussion

6.1 Main findings

This work improves our understanding of chemsex practices in Montréal by describing chemsex and polysubstance use trends over time among gbMSM and transgender women. It also provides information on the impact of chemsex on HIV prevention by examining its association with PrEP trajectories. Lastly, it strengthens existing evidence on the impact of chemsex on STI transmission by estimating the impact of these practices among gbMSM and transgender women using PrEP.

The first manuscript provides an up-to-date description of chemsex in Montréal among gbMSM consulting for PrEP. The results showed that chemsex is prevalent among gbMSM and transgender women consulting for PrEP in Montréal and that substance use patterns are similar to those in some European countries. Among gbMSM and transgender women consulting for PrEP between 2013–2020, 24% reported chemsex in the P12M and 13% reported two or more chemsex substances. Chemsex prevalence decreased from 38% in 2014 to 10% in 2019. This adds to our previous understanding of chemsex and SDU in Montréal [14,28,29] by presenting clear data on these practices for HIV-negative gbMSM in the city. These findings highlight a need for tailored interventions and could help inform service and program development.

The first manuscript also provides clear evidence that reporting chemsex at baseline is not a barrier to PrEP initiation or persistence in a large cohort composed mostly of gbMSM. The proportion of clients who initiated PrEP was nearly identical (73%) regardless of whether clients reported chemsex at baseline, and median time to discontinuation was slightly less than 7 months in both groups. This comparison was unaffected by the PrEP regimen prescribed at baseline, and clients reporting polysubstance use also had similar PrEP trajectories to those not reporting chemsex. Previous studies had shown that chemsex is not associated with poorer PrEP adherence [69,70], but these were limited by their small sample size and the fact that they used data from clinical trials.

The second manuscript adds to our growing understanding of the syndemic of substance use and STI transmission among gbMSM by highlighting a strong link between chemsex at

baseline and incident STI diagnoses. It also improves upon previous cross-sectional studies [8,10,11,19] by establishing a clear temporal link in the chemsex-STI relationship. Among gbMSM and transgender women using PrEP in Montréal, chemsex at baseline was linked to a 32% (95% CI: 10–57%) higher hazard of diagnosis of gonorrhea or chlamydia, equivalent to a risk increase of 8.9-percentage points (95% CI: 8.5–9.4) 12 months after PrEP initiation. This effect was stronger for gonorrhea alone, suggesting that the effect of chemsex on STI incidence may be due to certain specific sexual practices [89,90]. Additionally, there was one incident HCV infection observed in the chemsex group and none in the no-chemsex group. Despite the high incidence of STIs in the cohort, there were no incident HIV diagnoses. The manuscript also shows that polysubstance use and canonical chemsex substances like crystal meth and GHB have a stronger impact on STI incidence. Effect modification analyses suggest that the magnitude of the effect of chemsex on STI acquisition is heterogeneous across age, education, and income levels. These differences could be due to differences in substance use patterns and harm reduction strategies used during chemsex. The high STI incidence and lack of incident HIV infections suggest that PrEP is meeting a harm reduction need for men who practice chemsex, in line with a combination approach to HIV prevention [91]. However, the high STI incidence also highlights unmet prevention needs among gbMSM who practice chemsex. Understanding the heterogeneity of how chemsex affects STI transmission will help to develop services and interventions to better address the diversity of chemsex practices among gbMSM.

6.2 Strengths and limitations

The results presented in this thesis benefit from several strengths. Behavioural and STI data was prospectively collected, and clients were specifically asked about their substance use in sexual contexts, reducing potential recall bias and exposure misclassification. This work also leverages data collected over seven years on nearly 3,000 clients at l'Actuel, facilitating granular analyses of chemsex trends over time and of the effect of chemsex on STI acquisition. The use of regular STI screening, laboratory-confirmed STI diagnosis data and data on site of infection also enabled detailed analyses of the chemsex-STI relationship.

There are also various limitations that should be kept in mind when considering these findings. For the first manuscript, given that data came from a clinical cohort of PrEP users, the PrEP cascade prior to consultation could not be characterized. Similarly, these analyses did not

characterize reasons for non-initiation and discontinuation of PrEP. The analyses of PrEP trajectory also used a strict definition of discontinuation and did not capture PrEP re-initiation.

For the second manuscript, the dynamic nature of PrEP use meant that there was substantial loss to follow-up due to PrEP discontinuation. Additionally, data on chemsex was only collected at baseline and there was no measure of frequency. These shortcomings were alleviated by restricting follow-up to the first two years, and examination of the role of polysubstance use was still possible. Moreover, as manuscript 1 showed, attrition due to discontinuation was non-differential, so it is unlikely it introduced major bias. Lastly, the outcome was restricted to gonorrhea and chlamydia diagnoses as these are simpler to extract from clinical datasets. As such, incidence of syphilis –another bacterial infection showing a concerning trend among gbMSM– was not considered. Although HCV incidence was examined, no conclusions can be drawn from the single seroconversion that was observed in this study.

There are also limitations in how much of a causal relationship this study can establish between chemsex and STI incidence. First, despite adjusting for sociodemographic confounders, unmeasured confounding remains possible. Second, we cannot rule out some exposure misclassification since chemsex was only measured at baseline, chemsex reporting could be influenced by social desirability bias (i.e., clients not reporting chemsex due to perceived stigma), and the chemsex question did not explicitly ask whether substances were used intentionally for sex. This misclassification could be non-differential with respect to STI outcome ascertainment and would bias the estimates towards the null. In addition, the third kind of misclassification would mostly impact a fraction of the clients who only reported cocaine, ecstasy, and/or crack (n = 173), as the other chemsex substances (GHB, crystal meth, ketamine) are used predominantly for sex among gbMSM. Given the strength of the relationship in this study and the consistency of the results with previous research, it is unlikely that these limitations pose a major threat to the qualitative conclusions derived from these findings.

A shortcoming for all analyses was the small number of transgender women included, which precluded stratified analyses.

6.3 Areas for future research

This thesis improves our understanding of chemsex practices among gbMSM and their impacts on PrEP use and STI incidence, but various knowledge gaps remain to improve existing

services and develop new ones. Future studies should aim to quantify frequency of chemsex practices among gbMSM, which were not captured in the l'Actuel data. More detailed analyses are also needed to understand the role of chemsex at all stages of the PrEP cascade –not just after consultation– and to identify barriers to access.

An important contextual factor that could not be addressed in this study is the impact of venue on the types of chemsex sessions. It is possible that chemsex in certain venues is more predisposed to STI transmission and other harms, and this information could enable the development of more targeted and effective harm reduction interventions. Analyses should also look at incidence of syphilis and HCV infection, and the impact of chemsex on recurrence of infection. Lastly, this study highlights how unmet prevention needs arise from a syndemic of substance use and STI transmission, and the impacts of chemsex on mental health and psychosocial wellbeing should also be the investigated.

Research and services should also be devoted specifically to address the needs of transgender women. They were included in this study as it was assumed that they have similar sexual health risks if they are on PrEP, but they have unique needs and barriers that should be addressed independently.

Chapter 7

Conclusion

Chemsex is relatively prevalent among gbMSM and transgender women consulting for PrEP, with one in four clients reporting the practice at a large sexual health clinic in Montréal. Notably, chemsex is not an obstacle to PrEP initiation or retention, and there were no incident HIV infections in this cohort, showing that PrEP can meet a need for HIV prevention tools among gbMSM who practice chemsex. However, there was a high STI incidence in this cohort, and chemsex and polysubstance use at baseline were linked to higher risk of incident gonorrhea and chlamydia diagnosis. This effect was heterogeneous and varied according to substances reported, age, education, and income. These results highlight unmet prevention needs and call for further development of services that can address the intersection of substance use and sexual health. Future work is needed to develop and improve interventions for chemsex, to determine what men who practice chemsex want from such services, and to better ascertain what populations have the greatest unmet needs.

References

[1] Ghosn J, Taiwo B, Seedat S, Autran B, Katlama C. HIV. Lancet 2018;392:685–97. https://doi.org/10.1016/S0140-6736(18)31311-4.

[2] Bitera R, Alary M, Sylvain D. Programme de surveillance de l'infection par le virus de l'immunodéficience humaine (VIH) au Québec : rapport 2019. INSPQ; 2020.

[3] Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. Lancet 2017;389:941–50. https://doi.org/10.1016/S0140-6736(17)30003-X.

[4] Halkitis PN, Wolitski RJ, Millett GA. A holistic approach to addressing HIV infection disparities in gay, bisexual, and other men who have sex with men. Am Psychol 2013;68:261–73. https://doi.org/10.1037/a0032746.

[5] Bourne A, Reid D, Hickson F, Torres Rueda S, Weatherburn P. The Chemsex study: drug use in sexual settings among gay and bisexual men in Lambeth, Southwark and Lewisham. London: Sigma Research, London School of Hygiene & Tropical Medicine; 2014.

[6] McCall H, Adams N, Mason D, Willis J. What is chemsex and why does it matter? BMJ 2015;351. https://doi.org/10.1136/bmj.h5790.

[7] Stuart D. Chemsex: origins of the word, a history of the phenomenon and a respect to the culture. Drugs Alcohol Today 2019;19:3–10. https://doi.org/10.1108/DAT-10-2018-0058.

[8] Curtis TJ, Rodger AJ, Burns F, Nardone A, Copas A, Wayal S. Patterns of sexualised recreational drug use and its association with risk behaviours and sexual health outcomes in men who have sex with men in London, UK: a comparison of cross-sectional studies conducted in 2013 and 2016. Sex Transm Infect 2020;96:197–203. https://doi.org/10.1136/sextrans-2019-054139.

[9] Grov C, Westmoreland D, Morrison C, Carrico AW, Nash D. The Crisis We Are Not Talking About: One-in-Three Annual HIV Seroconversions Among Sexual and Gender Minorities Were Persistent Methamphetamine Users. J Acquir Immune Defic Syndr 2020;85:272–9. https://doi.org/10.1097/QAI.0000000000002461.

[10] Ottaway Z, Finnerty F, Amlani A, Pinto-Sander N, Szanyi J, Richardson D. Men who have sex with men diagnosed with a sexually transmitted infection are significantly more likely to engage in sexualised drug use. Int J STD AIDS 2017;28:91–3. https://doi.org/10.1177/0956462416666753.

[11] Pufall EL, Kall M, Shahmanesh M, Nardone A, Gilson R, Delpech V, et al. Sexualized drug use ('chemsex') and high-risk sexual behaviours in HIV-positive men who have sex with men. HIV Med 2018;19:261–70. https://doi.org/10.1111/hiv.12574.

[12] Pakianathan M, Whittaker W, Lee MJ, Avery J, Green S, Nathan B, et al. Chemsex and new HIV diagnosis in gay, bisexual and other men who have sex with men attending sexual health clinics. HIV Med 2018;19:485–90. https://doi.org/10.1111/hiv.12629.

[13] Brogan N, Paquette DM, Lachowsky NJ, Blais M, Brennan DJ, Hart TA, et al. Canadian results from the European Men-who-have-sex-with-men Internet survey (EMIS-2017). Can Commun Dis Rep 2019;45:271–82. https://doi.org/10.14745/ccdr.v45i11a01.

[14] Messier-Peet M, Herak Apelian, Gilles Lambert, Joseph Cox. Chemsex & Mental Health in gbMSM in Montreal: Results from Engage Cycle 1 2018.

[15] Direction générale de la santé publique. La prophylaxie préexposition au virus de l'immunodéficience humaine : Guide pour les professionnels de la santé du Québec. Ministère de la Santé et des Services sociaux; 2019.

[16] Tan DHS, Hull MW, Yoong D, Tremblay C, O'Byrne P, Thomas R, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. CMAJ 2017;189:E1448–58. https://doi.org/10.1503/cmaj.170494.
[17] Scott HM, Klausner JD. Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US. AIDS Res Ther 2016;13:5. https://doi.org/10.1186/s12981-016-0089-8.
[18] Maxwell S, Shahmanesh M, Gafos M. Chemsex behaviours among men who have sex with men: A systematic review of the literature. Int J Drug Policy 2019;63:74–89. https://doi.org/10.1016/j.drugpo.2018.11.014.
[19] Guerra FM, Salway TJ, Beckett R, Friedman L, Buchan SA. Review of sexualized drug use associated with sexually transmitted and blood-borne infections in gay, bisexual and other men who have sex with men. Drug Alcohol Depend 2020;216:108237. https://doi.org/10.1016/j.drugalcdep.2020.108237.
[20] Flores-Aranda J, Goyette M, Aubut V, Blanchette M, Pronovost F. Let's talk about chemsex and pleasure: the missing link in chemsex services. Drugs Alcohol Today 2019;19:189–96. https://doi.org/10.1108/DAT-10-2018-0045.
[21] Bourne A, Reid D, Hickson F, Torres-Rueda S, Steinberg P, Weatherburn P. "Chemsex" and harm reduction need among gay men in South London. Int J Drug Policy 2015;26:1171–6. https://doi.org/10.1016/j.drugpo.2015.07.013.
[22] Santoro P, Rodríguez R, Morales P, Morano A, Morán M. One "chemsex" or many? Types of chemsex sessions among gay and other men who have sex with men in Madrid, Spain: findings from a qualitative study. Int J Drug Policy 2020;82:102790. https://doi.org/10.1016/j.drugpo.2020.102790.
[23] Hawkins BW, Armstrong HL, Kesselring S, Rich AJ, Cui Z, Sereda P, et al. Substance Use as a Mechanism for Social Inclusion among Gay, Bisexual, and Other Men Who Have Sex with Men in Vancouver, Canada. Subst Use Misuse 2019;54:1945–55. https://doi.org/10.1080/10826084.2019.1621901.
[24] Blomquist PB, Mohammed H, Mikhail A, Weatherburn P, Reid D, Wayal S, et al. Characteristics and sexual health service use of MSM engaging in chemsex: results from a large online survey in England. Sex Transm Infect 2020. https://doi.org/10.1136/sextrans-2019-054345.
[25] Sewell J, Miltz A, Lampe FC, Cambiano V, Speakman A, Phillips AN, et al. Poly drug use, chemsex drug use, and associations with sexual risk behaviour in HIV-negative men who have sex with men attending sexual health clinics. Int J Drug Policy 2017;43:33–43. https://doi.org/10.1016/j.drugpo.2017.01.001.
[26] Hampel B, Kusejko K, Kouyos RD, Böni J, Flepp M, Stöckle M, et al. Chemsex drugs on the rise: a longitudinal analysis of the Swiss HIV Cohort Study from 2007 to 2017. HIV Med 2020;21:228–39. https://doi.org/10.1111/hiv.12821.
[27] Barrett P, O'Donnell K, Fitzgerald M, Schmidt AJ, Hickson F, Quinlan M, et al. Drug use among men who have sex with men in Ireland: Prevalence and associated factors from a national online survey. Int J Drug Policy 2019;64:5–12. https://doi.org/10.1016/j.drugpo.2018.11.011.
[28] Lambert G, Cox J, Tremblay F, M-A G, Frigault L, Tremblay C, et al. ARGUS 2005 : Sommaire de l'enquête sur l'infection au VIH, les hépatites virales et les infections transmissibles sexuellement et par le sang (ITSS) ainsi que sur les comportements à risques associés chez les hommes de Montréal ayant des relations sexuelles avec des hommes

(HARSAH). Montréal: Direction de santé publique de Montréal, Institut national de santé publique du Québec et Agence canadienne de santé publique; 2006.
[29] Lambert G, Cox J, Miangotar Y, Tremblay C, Alary M, Otis J, et al. ARGUS Cycle 2008-2009 : Faits saillants. Montréal: Direction de santé publique de Montréal, Institut national de santé publique du Québec et Agence canadienne de santé publique; 2011.
[30] Noor SW, Adam BD, Brennan DJ, Moskowitz DA, Gardner S, Hart TA. Scenes as Micro-Cultures: Examining Heterogeneity of HIV Risk Behavior Among Gay, Bisexual, and Other Men Who Have Sex with Men in Toronto, Canada. Arch Sex Behav 2018;47:309–21. https://doi.org/10.1007/s10508-017-0948-y.
[31] Lafortune D, Blais M, Miller G, Dion L, Lalonde F, Dargis L. Psychological and Interpersonal Factors Associated with Sexualized Drug Use Among Men Who Have Sex with Men: A Mixed-Methods Systematic Review. Arch Sex Behav 2020. https://doi.org/10.1007/s10508-020-01741-8.
[32] Bourne A, Reid D, Hickson F, Torres-Rueda S, Weatherburn P. Illicit drug use in sexual settings ('chemsex') and HIV/STI transmission risk behaviour among gay men in South London: findings from a qualitative study. Sex Transm Infect 2015;91:564–8. https://doi.org/10.1136/sextrans-2015-052052.
[33] Celentano DD, Valleroy LA, Sifakis F, MacKellar DA, Hylton J, Thiede H, et al. Associations Between Substance Use and Sexual Risk Among Very Young Men Who Have Sex With Men. Sex Transm Dis 2006;33:265–71. https://doi.org/10.1097/01.olq.0000187207.10992.4e.
[34] Colfax G, Vittinghoff E, Husnik MJ, McKirnan D, Buchbinder S, Koblin B, et al. Substance Use and Sexual Risk: A Participant- and Episode-level Analysis among a Cohort of Men Who Have Sex with Men. Am J Epidemiol 2004;159:1002–12. https://doi.org/10.1093/aje/kwh135.
[35] Blais M, Otis J, Lambert G, Cox J, Haig T, Groupe de recherche Spot. Consommation de substances en contexte sexuel chez des hommes gbHSH de Montréal : 2009-2016. Drogues, santé et société 2018;17:76. https://doi.org/10.7202/1062117ar.
[36] Hammoud MA, Vaccher S, Jin F, Bourne A, Haire B, Maher L, et al. The new MTV generation: Using methamphetamine, Truvada™, and Viagra™ to enhance sex and stay safe. Int J Drug Policy 2018;55:197–204. https://doi.org/10.1016/j.drugpo.2018.02.021.
[37] Vu NTT, Holt M, Phan HTT, La LT, Tran GM, Doan TT, et al. The Relationship Between Methamphetamine Use, Sexual Sensation Seeking and Condomless Anal Intercourse Among Men Who Have Sex With Men in Vietnam: Results of a Community-Based, Cross-Sectional Study. AIDS Behav 2017;21:1105–16. https://doi.org/10.1007/s10461-016-1467-x.
[38] De Baetselier I, Reyniers T, Platteau T, Wouters K, Nöstlinger C, Cuylaerts V, et al. Recurrent sexually transmitted infections among a cohort of men who have sex with men using pre-exposure prophylaxis in Belgium are highly associated with sexualized drug use. Sex Transm Dis 2021;Publish Ahead of Print. https://doi.org/10.1097/OLQ.0000000000001424.
[39] Grewal R, Allen VG, Gardner S, Moravan V, Tan DHS, Raboud J, et al. Serosorting and recreational drug use are risk factors for diagnosis of genital infection with chlamydia and gonorrhoea among HIV-positive men who have sex with men: results from a clinical cohort in Ontario, Canada. Sex Transm Infect 2017;93:71–5. https://doi.org/10.1136/sextrans-2015-052500.

[40] Evers YJ, Liere GAFSV, Hoebe CJPA, Dukers-Muijrers NHTM. Chemsex among men who have sex with men living outside major cities and associations with sexually transmitted infections: A cross-sectional study in the Netherlands. PLOS ONE 2019;14:e0216732. https://doi.org/10.1371/journal.pone.0216732.
[41] Tomkins A, Ahmad S, Cannon L, Higgins SP, Kliner M, Kolyva A, et al. Prevalence of recreational drug use reported by men who have sex with men attending sexual health clinics in Manchester, UK. Int J STD AIDS 2018;29:350–6. https://doi.org/10.1177/0956462417725638.
[42] Chow EPF, Grulich AE, Fairley CK. Epidemiology and prevention of sexually transmitted infections in men who have sex with men at risk of HIV. Lancet HIV 2019;6:e396–405. https://doi.org/10.1016/S2352-3018(19)30043-8.
[43] Public Health Agency of Canada. Report on sexually transmitted infections in Canada, 2017. Public Health Agency of Canada; 2019.
[44] Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Gonorrhea in Canada, 2010–2015. Can Commun Dis Rep 2018;44:37–42. https://doi.org/10.14745/ccdr.v44i02a01.
[45] Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Infectious and congenital syphilis in Canada, 2010–2015. Can Commun Dis Rep 2018;44:43–8. https://doi.org/10.14745/ccdr.v44i02a02.
[46] Choudhri Y, Miller J, Sandhu J, Leon A, Aho J. Chlamydia in Canada, 2010–2015. Can Commun Dis Rep 2018;44:49–54. https://doi.org/10.14745/ccdr.v44i02a03.
[47] Unemo M, Bradshaw CS, Hocking JS, de Vries HJC, Francis SC, Mabey D, et al. Sexually transmitted infections: challenges ahead. The Lancet Infectious Diseases 2017;17:e235–79. https://doi.org/10.1016/S1473-3099(17)30310-9.
[48] Blouin K, Lambert G, Venne S. Portrait des infections transmissibles sexuellement et par le sang (ITSS) au Québec : année 2018 et projections 2019. INSPQ; 2019.
[49] Unemo M, Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and Mycoplasma genitalium. Nat Rev Urol 2017;14:139–52. https://doi.org/10.1038/nrurol.2016.268.
[50] Flores-Aranda J, Goyette M, Larose-Osterrath C. Online Intervention as Strategy to Reach Men Who Have Sex With Other Men and Who Use Substances in a Sexual Context. Development of the MONBUZZ.ca Project. Front Psychiatry 2019;10:183. https://doi.org/10.3389/fpsyt.2019.00183.
[51] Stardust Z, Kolstee J, Joksic S, Gray J, Hannan S. A community-led, harm-reduction approach to chemsex: case study from Australia's largest gay city. Sex Health 2018;15:179. https://doi.org/10.1071/SH17145.
[52] Stuart D, Weymann J. ChemSex and care-planning: One year in practice. HIV Nursing 2015;15:24–8.
[53] Salway T, Ferlatte O, Shoveller J, Purdie A, Grennan T, Tan DHS, et al. The Need and Desire for Mental Health and Substance Use-Related Services Among Clients of Publicly Funded Sexually Transmitted Infection Clinics in Vancouver, Canada. J Public Health Manag Pract 2019;25:E1–10. https://doi.org/10.1097/PHH.0000000000000904.
[54] Spinner CD, Boesecke C, Zink A, Jessen H, Stellbrink H-J, Rockstroh JK, et al. HIV pre-exposure prophylaxis (PrEP): a review of current knowledge of oral systemic HIV PrEP in humans. Infection 2016;44:151–8. https://doi.org/10.1007/s15010-015-0850-2.

[55] Health Canada. Regulatory Decision Summary - TRUVADA 2016. https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?linkID=RDS00107 (accessed February 20, 2021).
[56] Direction générale de la santé publique. Avis intérimaire sur la prophylaxie préexposition au virus de l'immunodéficience humaine. Ministère de la Santé et des Services sociaux; 2013.
[57] Hull MW, Tan DHS. Setting the stage for expanding HIV pre-exposure prophylaxis use in Canada. Can Commun Dis Rep 2017;43:272–8. https://doi.org/10.14745/ccdr.v43i12a05.
[58] Greenwald ZR, Maheu-Giroux M, Szabo J, Robin JAB, Boissonnault M, Nguyen V-K, et al. Cohort profile: l'Actuel Pre-Exposure Prophylaxis (PrEP) Cohort study in Montreal, Canada. BMJ Open 2019;9. https://doi.org/10.1136/bmjopen-2018-028768.
[59] Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a Clinical Screening Index Predictive of Incident HIV Infection Among Men Who Have Sex With Men in the United States. JAIDS Journal of Acquired Immune Deficiency Syndromes 2012;60:421–7. https://doi.org/10.1097/QAI.0b013e318256b2f6.
[60] Alaei K, Paynter CA, Juan S-C, Alaei A. Using preexposure prophylaxis, losing condoms? Preexposure prophylaxis promotion may undermine safe sex. AIDS 2016;30:2753–6. https://doi.org/10.1097/QAD.0000000000001262.
[61] Hoornenborg E, Coyer L, van Laarhoven A, Achterbergh R, de Vries H, Prins M, et al. Change in sexual risk behaviour after 6 months of pre-exposure prophylaxis use: results from the Amsterdam pre-exposure prophylaxis demonstration project. AIDS 2018;32:1527–32. https://doi.org/10.1097/QAD.0000000000001874.
[62] Nguyen V-K, Greenwald ZR, Trottier H, Cadieux M, Goyette A, Beauchemin M, et al. Incidence of sexually transmitted infections before and after preexposure prophylaxis for HIV. AIDS 2018;32:523–30. https://doi.org/10.1097/QAD.0000000000001718.
[63] Traeger MW, Schroeder SE, Wright EJ, Hellard ME, Cornelisse VJ, Doyle JS, et al. Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis. Clin Infect Dis 2018;67:676–86. https://doi.org/10.1093/cid/ciy182.
[64] Traeger MW, Cornelisse VJ, Asselin J, Price B, Roth NJ, Willcox J, et al. Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infections Among Individuals at High Risk of HIV Infection. JAMA 2019;321:1380. https://doi.org/10.1001/jama.2019.2947.
[65] Marcus JL, Katz KA, Krakower DS, Calabrese SK. Risk Compensation and Clinical Decision Making — The Case of HIV Preexposure Prophylaxis. N Engl J Med 2019;380:510–2. https://doi.org/10.1056/NEJMp1810743.
[66] Marcus JL, Volk JE, Snowden JM. Concerns about a study on sexually transmitted infections after initiation of HIV preexposure prophylaxis. AIDS 2018;32:955–6. https://doi.org/10.1097/QAD.0000000000001769.
[67] Closson EF, Mitty JA, Malone J, Mayer KH, Mimiaga MJ. Exploring strategies for PrEP adherence and dosing preferences in the context of sexualized recreational drug use among MSM: a qualitative study. AIDS Care 2018;30:191–8. https://doi.org/10.1080/09540121.2017.1360992.
[68] Wade Taylor S, Mayer KH, Elsesser SM, Mimiaga MJ, O'Cleirigh C, Safren SA. Optimizing Content for Pre-exposure Prophylaxis (PrEP) Counseling for Men Who Have

Sex with Men: Perspectives of PrEP Users and High-Risk PrEP Naïve Men. AIDS Behav 2014;18:871–9. https://doi.org/10.1007/s10461-013-0617-7.
[69] O'Halloran C, Rice B, White E, Desai M, Dunn DT, McCormack S, et al. Chemsex is not a barrier to self-reported daily PrEP adherence among PROUD study participants. Int J Drug Policy 2019;74:246–54. https://doi.org/10.1016/j.drugpo.2019.10.007.
[70] Roux P, Fressard L, Suzan-Monti M, Chas J, Sagaon-Teyssier L, Capitant C, et al. Is on-Demand HIV Pre-exposure Prophylaxis a Suitable Tool for Men Who Have Sex With Men Who Practice Chemsex? Results From a Substudy of the ANRS-IPERGAY Trial. J Acquir Immune Defic Syndr 2018;79:e69. https://doi.org/10.1097/QAI.0000000000001781.
[71] Hojilla JC, Vlahov D, Crouch P-C, Dawson-Rose C, Freeborn K, Carrico A. HIV Pre-exposure Prophylaxis (PrEP) Uptake and Retention Among Men Who Have Sex with Men in a Community-Based Sexual Health Clinic. AIDS Behav 2018;22:1096–9. https://doi.org/10.1007/s10461-017-2009-x.
[72] Xia Y, Greenwald ZR, Milwid RM, Trottier C, Boissonnault M, Gaul N, et al. Pre-exposure Prophylaxis Uptake Among Men Who Have Sex With Men Who Used nPEP: A Longitudinal Analysis of Attendees at a Large Sexual Health Clinic in Montréal (Canada). J Acquir Immune Defic Syndr 2020;85:408–15. https://doi.org/10.1097/QAI.0000000000002472.
[73] Sewell J, Cambiano V, Speakman A, Lampe FC, Phillips A, Stuart D, et al. Changes in chemsex and sexual behaviour over time, among a cohort of MSM in London and Brighton: Findings from the AURAH2 study. Int J Drug Policy 2019;68:54–61. https://doi.org/10.1016/j.drugpo.2019.03.021.
[74] Daskalopoulou M, Rodger A, Phillips AN, Sherr L, Speakman A, Collins S, et al. Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. Lancet HIV 2014;1:e22–31. https://doi.org/10.1016/S2352-3018(14)70001-3.
[75] Miettinen OS. Theoretical epidemiology: principles of occurrence research in medicine. New York: Wiley; 1985.
[76] Haberer JE, Bangsberg DR, Baeten JM, Curran K, Koechlin F, Amico KR, et al. Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. AIDS 2015;29:1277–85. https://doi.org/10.1097/QAD.0000000000000647.
[77] Moore DF. Applied Survival Analysis Using R. Springer International Publishing; 2016. https://doi.org/10.1007/978-3-319-31245-3.
[78] Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. Springer International Publishing; 2000.
[79] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–99. https://doi.org/10.1002/sim.4067.
[80] Buuren S van, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw 2011;45:1–67. https://doi.org/10.18637/jss.v045.i03.
[81] Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. J Clin Epidemiol 2010;63:46–55. https://doi.org/10.1016/j.jclinepi.2009.03.012.
[82] Schomaker M, Heumann C. Bootstrap inference when using multiple imputation. Statistics in Medicine 2018;37:2252–66. https://doi.org/10.1002/sim.7654.
[83] Li R, Chambless L. Test for Additive Interaction in Proportional Hazards Models. Ann Epidemiol 2007;17:227–36. https://doi.org/10.1016/j.annepidem.2006.10.009.

[84] Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol 2012;41:514–20. https://doi.org/10.1093/ije/dyr218.
[85] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
[86] Kassambara A, Kosinski M, Biecek P, Fabian S. survminer: Drawing Survival Curves using "ggplot2." 2019.
[87] Therneau TM. survival: A Package for Survival Analysis in R. 2019.
[88] Buuren S van, Groothuis-Oudshoorn K, Vink G, Schouten R, Robitzsch A, Rockenschaub P, et al. mice: Multivariate Imputation by Chained Equations. 2021.
[89] Barbee LA, Khosropour CM, Dombrowski JC, Manhart LE, Golden MR. An estimate of the proportion of symptomatic gonococcal, chlamydial and non-gonococcal non-chlamydial urethritis attributable to oral sex among men who have sex with men: a case–control study. Sex Transm Infect 2016;92:155–60. https://doi.org/10.1136/sextrans-2015-052214.
[90] Chow EPF, Fairley CK. The role of saliva in gonorrhoea and chlamydia transmission to extragenital sites among men who have sex with men: new insights into transmission. J Int AIDS Soc 2019;22 Suppl 6:e25354. https://doi.org/10.1002/jia2.25354.
[91] Doyle CM, Maheu-Giroux M, Lambert G, Mishra S, Apelian H, Messier-Peet M, et al. Combination HIV Prevention Strategies Among Montreal Gay, Bisexual, and Other Men Who Have Sex with Men in the PrEP Era: A Latent Class Analysis. AIDS Behav 2021;25:269–83. https://doi.org/10.1007/s10461-020-02965-4.

Appendix – Additional Methods

Calculation of the standard error for effect-modified hazard ratios

In order to present the within-strata hazard ratios as suggested by Knol and VanderWeele, model coefficients have to be summed, which requires accounting for the covariance between them. Below I present an example of how these calculations are done for the education variable. A similar process would apply to the age and income covariates, simply with additional dummy variables for their different levels.

I use a Cox proportional hazards model where chemsex is the exposure of interest (represented by the variable *chem* that is 1 for reporting chemsex at baseline and 0 otherwise) and the hypothetical effect modifier is educational attainment (represented by a variable *edu* that is 0 for having secondary education or less and 1 otherwise). Additionally, a product term between chemsex and education is introduced, and the effect-modification coefficient β_3 is estimated. The other covariates specified in the model are represented in vector notation as $\beta_c X_c$.

$$\log h_i(t) = \log h_0(t) + \beta_1 * chem + \beta_2 * edu + \beta_3 * chem * edu + \beta_c X_c$$

For the reference level, the effect-modified estimate is given simply by the coefficient for chemsex. Consider an individual *j* with secondary education or less and chemsex = 1

$$\log h_j(t) = \log h_0(t) + \beta_1 * 1 + \beta_2 * 0 + \beta_3 * 1 * 0 + \beta_c X_j = \log h_0(t) + \beta_1 + \beta_c X_j$$

compared to a similar individual *k* with secondary education or less and chemsex = 0

$$\log h_k(t) = \log h_0(t) + \beta_1 * 0 + \beta_2 * 0 + \beta_3 * 1 * 0 + \beta_c X_j = \log h_0(t) + \beta_c X_j$$

Hence the effect for chemsex at university level is given by β_1, and constructing confidence intervals can be made simply by using the standard errors for this coefficient and then transforming into the hazard-ratio scale.

The calculations for any level other than the reference is slightly more complex and requires taking into account the covariance between coefficients. Consider now that individual *j* has post-secondary education and chemsex = 1

$$\log h_j(t) = \log h_0(t) + \beta_1 * 1 + \beta_2 * 1 + \beta_3 * 1 * 1 + \beta_c X_j = \log h_0(t) + \beta_1 + \beta_2 + \beta_3 + \beta_c X_j$$

compared to an individual *k* with the same covariates (including education) but chemsex = 0

$$\log h_k(t) = \log h_0(t) + \beta_1 * 0 + \beta_2 * 1 + \beta_3 * 0 * 1 + \beta_c X_j = \log h_0(t) + \beta_2 + \beta_c X_j$$

Hence the effect for chemsex at post-secondary level is given by $\beta_1 + \beta_3$. The standard error for this sum can be estimated as

$$SE(\beta_1 + \beta_3) = \sqrt{SE(\beta_1)^2 + SE(\beta_3)^2 + 2 * cov(\beta_1, \beta_3)}$$

where $SE(z)$ is the standard error of z and $cov(z, w)$ is the covariance between z and w. This estimated standard error can thus be used to compute the confidence intervals shown in Table 3 of the second manuscript.

List of R packages used

Data analysis

Buuren S van, Groothuis-Oudshoorn K, Vink G, et al. **mice: Multivariate Imputation by Chained Equations**. 2021 [cited 2021 Jun 16]. Available from: https://CRAN.R-project.org/package=mice

Therneau TM, Thomas Lumley (original S.->R port and R. maintainer until 2009), Elizabeth A, Cynthia C. **survival: Survival Analysis**. 2019 [cited 2020 Dec 23]. Available from: https://CRAN.R-project.org/package=survival

Data visualization

Auguie B, Antonov A. **gridExtra: Miscellaneous Functions for "Grid" Graphics**. 2017 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=gridExtra

Garnier S, Ross N, Rudis B, Sciaini M, Scherer C. **viridis: Default Color Maps from "matplotlib"**. 2018 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=viridis

Kassambara A, Kosinski M, Biecek P, Fabian S. **survminer: Drawing Survival Curves using "ggplot2"**. 2019 [cited 2020 Dec 23]. Available from: https://CRAN.R-project.org/package=survminer

Neuwirth E. **RColorBrewer: ColorBrewer Palettes**. 2014 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=RColorBrewer

Wickham H, Chang W, Henry L, Pedersen TL, Takahashi K, Wilke C, et al. **ggplot2: Create Elegant Data Visualisations Using the Grammar of Graphics**. 2019 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=ggplot2

Xie Y, Vogt A, Andrew A, Zvoleff A, Andre Simon (the CSS files under inst/themes/ were derived from the Highlight package http://www.andre-simon.de), Atkins A, et al. **knitr: A General-Purpose Package for Dynamic Report Generation in R**. 2020 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=knitr

Zhu H, Travison T, Tsai T, Beasley W, Xie Y, Yu G, et al. **kableExtra: Construct Complex Table with "kable" and Pipe Syntax**. 2019 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=kableExtra

Data cleaning and manipulation

Firke S, Denney B, Haid C, Knight R, Grosser M, Zadra J. **janitor: Simple Tools for Examining and Cleaning Dirty Data**. 2020 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=janitor

Robinson D, Hayes A, Couch S, Patil I, Chiu D, Gomez M, et al. **broom: Convert Statistical Objects into Tidy Tibbles**. 2020 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=broom

Spinu V, Grolemund G, Wickham H, Lyttle I, Costigan I, Law J, et al. **lubridate: Make Dealing with Dates a Little Easier**. 2018 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=lubridate

Wickham H, François R, Henry L, Müller K, RStudio. **dplyr: A Grammar of Data Manipulation**. 2020 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=dplyr

Wickham H, RStudio. **forcats: Tools for Working with Categorical Variables (Factors)**. 2019 [cited 2021 Apr 13]. Available from: https://CRAN.R-project.org/package=forcats