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1. 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 of event) 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

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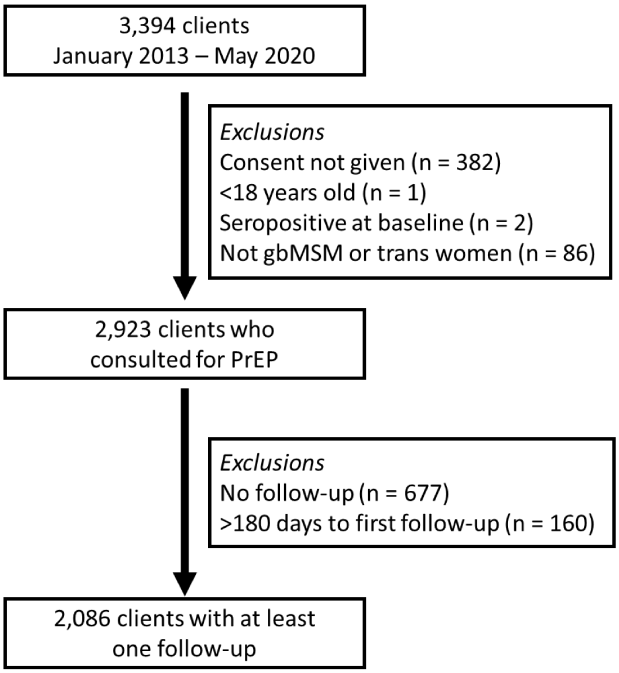
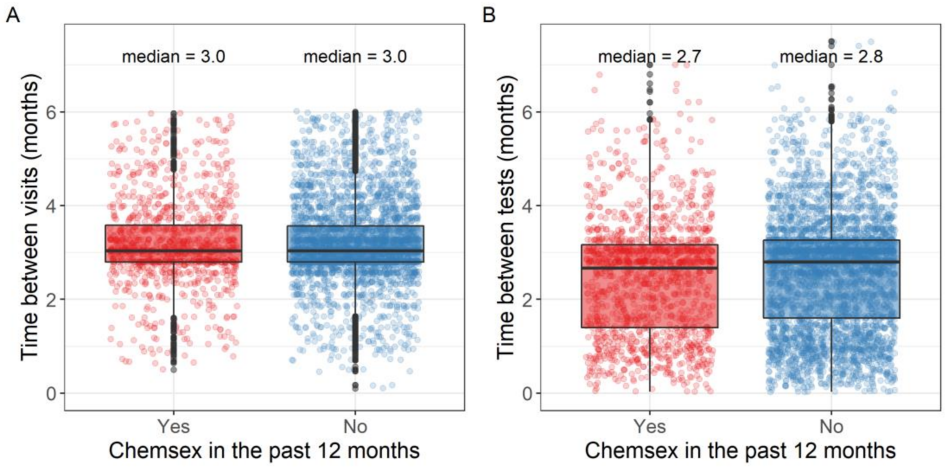
2. Supplementary results



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: Distribution of A) time between PrEP follow-up visits and B) time between tests for sexually transmitted infections (STI) among pre-exposure prophylaxis (PrEP) users in the l'Actuel PrEP Cohort (2013-2020). Data for A) excludes time intervals between baseline and first follow-up, since the first follow-up visit was scheduled 1 month after the baseline visit whereas subsequent follow-up visits were scheduled at 3-month intervals. For B), data includes time intervals for all STI testing visits that occurred up to 2 years after PrEP initiation.

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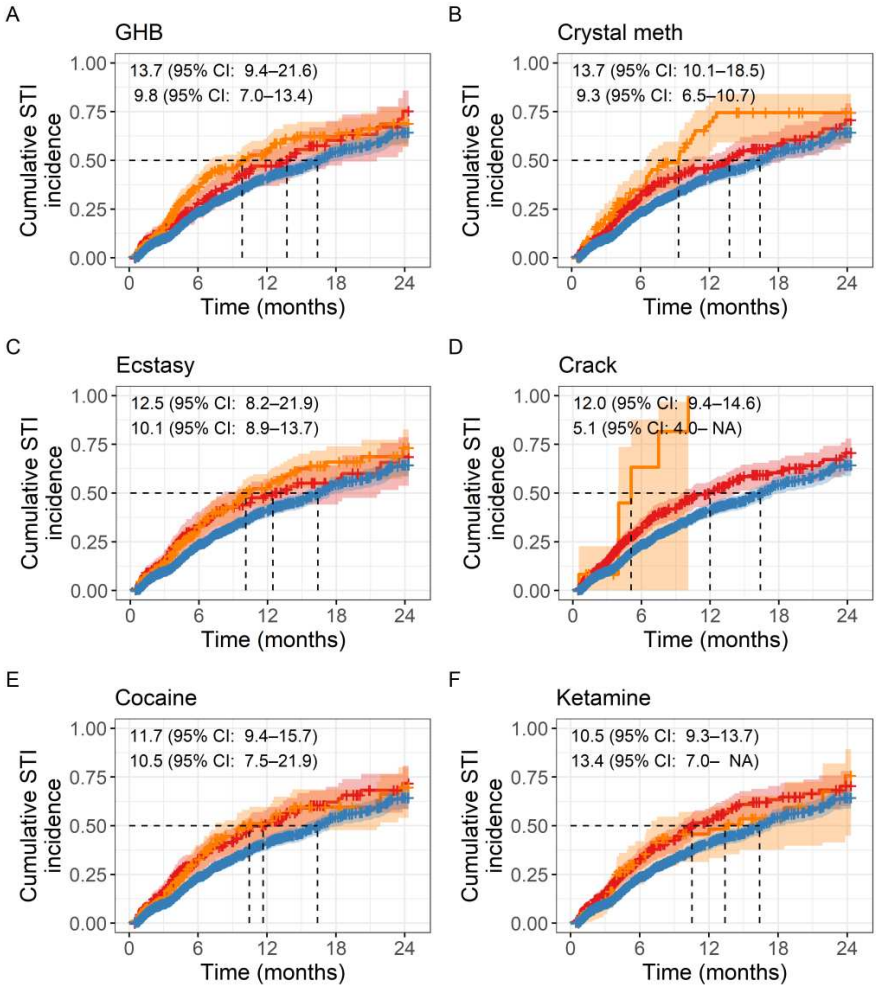

Supplementary Figure 3: Cumulative incidence of gonorrhea and chlamydia among pre-exposure prophylaxis (PrEP) users in the *l'Actuel PrEP Cohort* (2013-2020). For the six chemsex substances considered, the chemsex group was stratified into two sub-groups: individuals who reported chemsex including the 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.

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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				
≤$10,000 CAD	REF	–	–	–
$10,001–$20,000 CAD	0.85	(0.54 – 1.33)	0.228	0.47
$20,001–$35,000 CAD	0.96	(0.64 – 1.44)	0.203	0.849
$35,001–$55,000 CAD	0.89	(0.59 – 1.34)	0.207	0.562
$55,001–$75,000 CAD	0.85	(0.57 – 1.28)	0.205	0.444
≥$75,000 CAD	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; HR: hazard ratio; PrEP: pre-exposure prophylaxis.

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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)	1.62	(1.30 – 2.03)
Urethra	78	1.42	(0.88 – 2.29)	1.53	(0.92 – 2.53)
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)	0.99	(0.64 – 1.51)

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; PrEP: pre-exposure prophylaxis.

Supplementary Table 3: 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), excluding transgender participants.

		Crude models		Adjusted models	
Outcome	**# of events**	**HR**	**95% CI**	**HR**	**95% CI**
Model with chemsex only					
Gonorrhea or chlamydia	613	1.42	(1.19 – 1.69)	1.33	(1.11 – 1.59)
Gonorrhea	409	1.71	(1.40 – 2.11)	1.61	(1.30 – 1.99)
Chlamydia	369	1.16	(0.92 – 1.46)	1.08	(0.85 – 1.36)
Model with chemsex and polysubstance use					
Gonorrhea or chlamydia	613				
No chemsex		REF	–	–	–
Chemsex		1.21	(0.95 – 1.54)	1.13	(0.88 – 1.44)
Polysubstance use		1.62	(1.31 – 2.01)	1.54	(1.23 – 1.92)

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; PrEP: pre-exposure prophylaxis.