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Trajectories of injection drug use among people who use drugs in Vancouver, Canada, 1996–2017: growth mixture modeling using data from prospective cohort studies

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ABSTRACT

Background and aims Injection drug use patterns are known to change over time, although such long-term changes have not been well described. We sought to characterize longitudinal trajectories of injection drug use and identify associated factors. **Design** Data were derived from the Vancouver Injection Drug Users Study and AIDS Care Cohort to evaluate the Exposure to Survival Services study, two prospective cohorts involving people who inject drugs in Vancouver, Canada between 1996 and 2017. Growth mixture modeling was applied to identify distinct injection drug use trajectories. Multinomial logistic regression was used to identify baseline factors associated with each trajectory. **Setting** Canada. **Participants** A total of 2057 participants who reported having used illicit drugs via injection in the past 6 months at the baseline visit were included in the study. The median time since first injection drug use at baseline was 14.8 years (quartile 1–quartile 3: 6.5–24.3). **Measurements** Information regarding self-reported injection drug use during the past 6 months was collected at baseline and semi-annually thereafter via interviewer-administered questionnaires. **Findings** Participants were followed for a median of 113.4 months (quartile 1–quartile 3: 63.4–161.7). Five trajectories were identified: persistent high frequency injection (507, 24.6%); high frequency injection with late decrease (374, 18.2%); gradual cessation (662, 32.2%); early cessation with late relapse (227, 11.0%); and early cessation (287, 14.0%). Factors found to be associated with distinct trajectories included: daily heroin injection, binge injection drug use, age, not being in a stable relationship and year of study enrollment. **Conclusions** People who used drugs in Vancouver, Canada from 1996 to 2017 appeared to follow five drug use trajectories, ranging from persistent high frequency use to early cessation. Almost 25% of participants remained high-frequency injectors over the study period.

Keywords Cessation, injection drug use, relapse, growth mixture modeling, latent trajectory groups, longitudinal studies.

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INTRODUCTION

The impact of injection drug use on the health of individuals and related social harms continues to be significant. Globally, there are around 13 million people who inject drugs, of whom approximately 13% are living with HIV and 67% are seropositive for hepatitis C [1]. People who inject drugs also suffer from high rates of preventable morbidity and mortality. A recent systematic review including 67 cohorts involving people who inject drugs demonstrated a pooled crude mortality rate of 2.4 deaths per 100 person-years, which constitutes approximately 14.7 times the risk of death among the general population [2]. Untreated substance dependence also inflicts substantive economic and social harm on communities, including unemployment, lost productivity, criminal activity and excessive healthcare costs [3]. Therefore, reducing the prevalence of injection drug use remains an important public health challenge, which in turn requires a better understanding of the natural history of injection drug use.

Research demonstrates that over the course of a drug injection career, drug use patterns are rarely stable [4–9]. Multiple studies on drug use trajectories have focused on short-term (e.g. 6 months) injection drug use cessation and relapse, and suggested that factors including intensity of drug injection, frequent non-injection drug use, polydrug use, alcohol drinking, age at injection initiation, homelessness, incarceration, illegal income generating activities and treatment involvement play an important role in influencing injection behavior change [5,8,10–12].

However, substance dependence is a chronic relapsing condition, as a significant portion of people will experience multiple episodes of cessation of and relapse into active substance use over their drug-using career [13–15]. Few studies have provided insight into the factors associated with longitudinal patterns of injection drug use. Factors indicative of drug of choice and substance use severity (e.g. mixed heroin and cocaine injection, daily or more frequent injection, cumulative past use of stimulants), social stability (e.g. criminality, employment), treatment involvement (e.g. number of past treatment episodes) and psychological distress have been found to be predictors of change in long-term substance use patterns [14,16–19]. Interestingly, factors associated with short-term changes in injection behavior do not consistently predict long-term injection trajectories. For instance, numerous studies have documented that among those who cease use as a result of formal addiction treatment interventions, high rates of relapse are typical after treatment discharge [20–23]. Furthermore, for factors that are associated with both short- and long-term changes in injection behavior, the strength of the associations often varies. Specifically, a meta-analysis examined and summarized different types of predictors of continued drug use during and after treatment for opioid use disorder, and showed that for various factors (e.g. drug use history, criminal behavior), the strength of concurrent and longitudinal associations differs considerably [24].

To date, only a small number of studies have examined longitudinal trajectories of injection drug use behavior during periods of 10 years or greater. Two studies using a sample of people who use drugs in the AIDS Linked to the Intravenous Experience (ALIVE) cohort in Baltimore, United States [13,19] consistently found an overall decreasing trend of injection drug use, with a substantial proportion of people stopping injection for extended timeframes. Another recently published study assessed patterns of changes in injecting frequency in a European population and found similar longitudinal patterns [25], but the overall decreasing trend was not as strong as in the ALIVE cohort. In the face of escalating harmful illicit drug use, harm-reduction interventions, including needle and syringe programs [26], supervised consumption facilities [27] and methadone maintenance therapy [28,29], have been implemented and scaled-up in British Columbia, Canada. However, to our knowledge, there exist no studies that have examined the longitudinal trajectories of injection drug use in a Canadian setting.

Given that the long-term trajectories of injection drug use remain understudied, there are limited empirical examinations of the natural history of injection drug use. There is, however, considerable practical and scientific importance associated with gaining greater understanding of longitudinal trajectories of injection drug use which, in turn, will help provide scientific evidence to guide the development of strategies to reduce long-term injection drug use. Accordingly, this study aims to characterize long-term injection trajectories and identify factors associated with different injection drug use trajectories among long-standing cohorts of people who inject drugs in Vancouver, Canada.

METHODS

Design and participants

Data were derived from two ongoing open prospective cohort studies of people who use drugs in Vancouver: the Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). Detailed descriptions of these cohorts have been published elsewhere [30–32]. In brief, eligibility criteria for VIDUS includes being HIV-seronegative, at least 18 years of age at enrollment, residing in the Greater Vancouver area and reporting injecting an illicit drug in the month prior to enrollment. Eligibility criteria for ACCESS includes being HIV-seropositive, at least 18 years of age, residing in the Greater Vancouver area, and reporting using an illicit drug (other than or in addition to cannabis) in the month prior to enrollment. Recruitment for both cohorts relies on extensive snowball sampling, self-referral and street outreach. Individuals in VIDUS who seroconvert following recruitment are transferred to ACCESS for ongoing follow-up. The baseline and follow-up procedures for these studies, including the questionnaires, are harmonized to allow for combined analyses of the different cohorts.

At baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire that elicits a range of data. Nurses also assess participants for various health conditions and obtain blood samples for HIV and HCV serological testing, and HIV disease monitoring, as appropriate. Participants receive a $40 (CAD) honorarium for each visit. Both cohorts have received approvals from the University of British Columbia/Providence Health Care Research Ethics Board.

Eligibility criteria for the present study included: completing at least four follow-up visits between 1 May 1996 and 30 November 2017 to allow for polynomial growth

curve analysis and reporting having used illicit drugs via injection in the past 6 months at baseline.

Measures

The main outcome of interest was a time-varying dichotomous variable of self-reported injection drug use during the past 6 months (yes versus no). This was assessed by asking the participants: 'In the last 6 months, when you were using, which of the following drugs did you inject?'. The outcome variable was defined as 'yes' if participants indicated injecting substances including heroin alone, cocaine alone, heroin and cocaine, crystal methamphetamine, heroin and crystal meth, crack cocaine, fentanyl powder/pills, benzodiazipines, prescription opioids and any other specified drugs. We also sought to evaluate whether specific baseline individual characteristics, substance use behaviors and social–structural exposures were associated with different injection drug use trajectories. We included self-reported baseline characteristics, including age (per year decrease), sex (male versus female) and ethnicity (white versus others). Other socio-demographic factors included: education attainment (high school completion or higher versus less than high school); not being in a stable relationship, defined as not being married, common law or having a regular partner; employment, defined as having a regular job, temporary job or self-employed; and current housing status (unstable housing versus stable housing). Unstable housing was defined as living in a single-room occupancy hotel, shelter or other transitional housing or living on the street. Substance use factors were categorized as daily versus less than daily use, and included: heroin injection; stimulant (i.e. cocaine or crystal methamphetamine) injection; speedball injection (i.e. heroin and cocaine in combination); and prescription opioid injection. Non-injection drug use included crack cocaine use, cannabis use and alcohol use. Binge injection drug use (yes versus no) and years since injection drug use initiation were also included as substance use factors. Binge injection drug use was assessed using the survey question: 'In the last six months, did you go on runs or binges (that is, when you injected drugs more than usual)?'. Factors related to substance use treatment experience included: opioid agonist therapy (e.g. methadone maintenance treatment or buprenorphine/naloxone, yes versus no), any other addiction treatment or services except for opioid agonist therapy (yes versus no), as well as being unable to access addiction treatment (yes versus no). Other behavioral risk factors/outcomes and social–structural exposures were categorized as yes versus no, and included: being attacked, assaulted or suffered violence; drug dealing; sex work involvement; incarceration; and non-fatal overdose. All behavioral variables referred to the previous 6 months unless otherwise specified. We also included a variable asking participants if they have ever been diagnosed with a mental health issue (yes versus no), calendar year of study enrollment (per year increase) and study cohort designation (ACCESS versus VIDUS).

Statistical analysis

To identify the optimal number of groups, we applied growth mixture modeling (GMM), which is a semi-parametric, group-based analytical approach [33–35]. The objective of the model is to discover meaningful distinctive subpopulations with homogeneous longitudinal trajectories within the larger heterogeneous population.

The metric of time used for the GMM analysis was time since study enrollment due to the nature of our dynamic cohort study design. We started with a single-class latent growth curve model and continued until a six-class model was fitted. Linear, quadratic and cubic parameters were fitted for the time trend for each trajectory group. To avoid local maximization and ensure successful convergence, 500 random sets of starting values were used for each model. The models were compared using the following fit indices: Akaike information criterion (AIC), Bayesian information criterion (BIC) and Lo–Mendell–Rubin likelihood ratio test (LRT) [35,36]. Lower absolute values for the information criteria indices and significant LRT *P*-value suggest a better model fit. Averaged posterior probability of group membership and entropy were used to evaluate classification quality. Furthermore, to ensure interpretability and usefulness of the latent classes, sample size per latent class and substantive importance of the trajectory groups were also considered.

Then, we further evaluated whether or not any of the baseline individual characteristics, drug use behaviors or social–structural exposures would predict and help distinguish trajectory groups. To do so, we first summarized and compared the characteristics among trajectory groups, using Pearson's χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Next, we applied the standard three-step method, in which class membership was merged with the original data and used as an outcome in a multinomial logistic regression analysis [36]. We used an a priori-defined backward model selection procedure based on examination of AIC to fit a multivariable model. The multivariable model with the lowest AIC score was selected as the final model.

As a sensitivity analysis, we defined lost to follow-up as being alive but not seen within 3 years before the end of study period. Information on death, including date and underlying causes of death, was obtained through a confidential data linkage with the British Columbia Vital Statistics Agency. To assess the extent to which losses to follow-up and deaths affected the trajectory membership, we proceeded with the Roy latent dropout pattern-mixture

modeling [37,38], which can take into account potential non-ignorable dropout. For individuals who were lost to follow-up or died, their first missed study visit was treated as the time of dropout. Additionally, considering participants with various follow-up times, we conducted a second sensitivity analysis to examine the injection drug use trajectories among people with at least 10 years' follow-up time.

Data manipulations and multinomial regression analysis were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). GMM was applied using the software Mplus version 8 [39]. All *P*-values were two-sided.

RESULTS

General characteristics

Between May 1996 and November 2017, a total of 3146 individuals were enrolled into the cohorts. A total of 1089 were excluded from the present study: 236 did not report having injected drugs at baseline and 853 did not complete at least four follow-up visits. Compared with participants in the analytical sample (n = 2057), those excluded were younger at enrollment (median age = 34 years; $P < 0.001$), having injected drugs for fewer years (median time since injection drug use initiation: 9.5 years; $P < 0.001$), but there was no difference by sex (P = 0.098), ethnicity (P = 0.166) and risk of death (22.9%, P = 0.487).

Among 2057 included participants, 1309 (63.6%) were male, 1195 (58.1%) self-reported white ethnicity, and the median age was 37 years (quartile 1–quartile 3: 30–44). There were 740 participants who had ever been diagnosed with a mental health issue, and the most commonly reported diagnoses included depression (n = 441, 59.6%), anxiety (n = 163, 22.0%), bipolar disorder (n = 96, 13.0%), post-traumatic stress disorder (n = 90, 12.2%) and attention deficit disorder (n = 62, 8.4%). These participants contributed 36 679 observations with the median number of months between study visits as 6.0 (quartile 1–quartile 3: 5.7–6.8). The median time of follow-up per participant was 113.4 months (quartile 1–quartile 3: 63.4–161.7) and the median number of observations per participant was 16 visits (quartile 1–quartile 3: 9–23). Throughout the study period, the total number of identified deaths was 495, including 103 (20.8%) HIV-related deaths and 97 (19.6%) fatal overdose deaths; 462 (22.5%) participants were identified as lost to follow-up. Over time, there were 182 deaths and 181 dropouts observed within 5 years of follow-up, 188 deaths and 189 dropouts between the 6th to 10th years of follow-up, 81 deaths and 57 dropouts between the 11th to 15th years of follow-up and 44 deaths and 35 dropouts after the 15th year. Baseline demographic characteristics, behavioral factors and follow-up information are shown in Table 1.

Identify injection drug use trajectories

As shown in Table 2, different model fit statistics were compared with an increasing number of trajectories. Both AIC and BIC values continued to decrease, which was expected given the complexity of longitudinal data derived from this large sample. However, the reduction was relatively small when comparing models with four to six trajectory classes. LRT compared the likelihood of the model being tested with a model with one fewer class and suggested that the model was no longer improved with six classes (P = 0.515). Also taking into account the classification quality and interpretability, a five-class solution was chosen. The averaged posterior probability of group membership for the five-class solution is presented in Supporting information, Table S1. The trajectories of injection drug use are visualized in Fig. 1.

After assigning participants to each trajectory class based on their most likely latent class membership, we characterized the five classes as: (1) 'persistent injection' (n = 507, 24.6%); (2) 'persistent injection with late cessation' (n = 374, 18.2%); (3) 'gradual cessation' (n = 662, 32.2%); (4) 'early cessation with late relapse' (n = 227, 11.0%); and (5) 'early cessation' (287, 14.0%). The probability of injection drug use among the 'persistent injection' group remained high, ranging from 65.1 to 95.3% during the study period. For the 'persistent injection with late cessation' group, the probability of injection stayed relatively high (> 70.0%) until approximately the 18th year since baseline, and then showed a decreasing trend. We also observed three trajectory classes which represented distinctive injection cessation and relapse patterns. The probability of injection for 'gradual cessation' group declined steadily to approximately 25.0% during the study period. As shown in Fig. 1, the probability for the 'early cessation' group rapidly dropped to as low as 13.1% at the 6th year, then stayed below 10.0% after the 14th year and maintained less than 1.0% from the 16th year. The probability for the 'early cessation with late relapse' group also declined significantly at an early stage, with the lowest of 7.6% at the 12th year. However, it increased gradually afterwards showing a tendency towards relapse.

Baseline predictors of trajectory group membership

The results of bivariable and multivariable multinomial logistic regression analyses of factors associated with injection trajectories are presented in Table 3 and Table 4. Bivariable multinomial logistic regression analyses with the alternative trajectory group as the reference group are presented in Supporting information, Tables S2–S5. In the adjusted model, compared to the 'early cessation' group, participants of younger age were more likely to be

Table 1 Baseline demographic characteristics, drug use behaviors, social–structural exposures and follow-up information among 2057 people who use injection drugs, the Vancouver Injection Drug Users Study and AIDS Care Cohort to Evaluate Exposure to Survival Services, Vancouver, British Columbia, Canada, 1996–2017.

Characteristics	*Total n = 2057 (100%)*	*Persistent injection n = 507 (24.6%)*	*Persistent injection with late cessation n = 374 (18.2%)*	*Gradual cessation n = 662 (32.2%)*	*Early cessation with late relapse n = 227 (11.0%)*	*Early cessation n = 287 (14.0%)*	*P*
Socio-demographic factors							
Age (years), Median (quartile 1–quartile 3)	37 (30–44)	36 (28–43)	38 (30–44)	37 (31–44)	39 (29–44)	38 (31–45)	0.080
Male	1309 (63.6)	296 (58.4)	255 (68.2)	434 (65.6)	145 (63.9)	179 (62.4)	0.031
White ethnicity	1195 (58.1)	289 (57.0)	212 (56.7)	388 (58.6)	148 (65.2)	158 (55.1)	0.170
High school completion or higher	1387 (67.4)	345 (68.1)	236 (63.1)	419 (63.3)	176 (77.5)	211 (73.5)	< 0.001
Not being in a stable relationship[a]	1482 (72.1)	378 (74.6)	281 (75.1)	480 (72.5)	155 (68.3)	188 (65.5)	0.018
Employment status (regular/temporary job; self-employed)[a]	401 (19.5)	87 (17.2)	72 (19.3)	143 (21.6)	46 (20.3)	53 (18.5)	0.416
Unstable housing	1453 (70.6)	361 (71.2)	280 (74.9)	466 (70.4)	148 (65.2)	198 (69.0)	0.110
Substance use[a]							
Daily heroin injection	810 (39.4)	224 (44.2)	127 (34.0)	275 (41.5)	83 (36.6)	101 (35.2)	0.008
Daily stimulant injection	678 (33.0)	182 (35.9)	98 (26.2)	228 (34.4)	88 (38.8)	82 (28.6)	0.002
Daily speedball injection	249 (12.1)	80 (15.8)	33 (8.8)	79 (11.9)	26 (11.5)	31 (10.8)	0.029
Daily prescription opioid injection	78 (3.8)	12 (2.4)	20 (5.4)	29 (4.4)	7 (3.1)	10 (3.5)	0.177
Daily non-injection crack cocaine use	497 (24.2)	111 (21.9)	119 (31.8)	167 (25.2)	37 (16.3)	63 (22.0)	< 0.001
Daily cannabis use	393 (19.1)	93 (18.3)	87 (23.3)	112 (16.9)	45 (19.8)	56 (19.5)	0.164
Daily alcohol use	372 (18.1)	90 (17.8)	54 (14.4)	122 (18.4)	47 (20.7)	59 (20.6)	0.219
Binge injection drug use[b]	840 (40.8)	226 (44.6)	128 (34.2)	297 (44.9)	93 (41.0)	96 (33.5)	< 0.001
Years since injection drug use (quartile 1–quartile 3)	14.8 (6.5–24.3)	13.4 (5.2–24.1)	15.4 (7.4–24.5)	15.5 (7.2–23.7)	14.8 (6.6–25.9)	15.0 (5.7–24.9)	0.244
Treatment experience[a,b]							
Opioid agonist therapy	520 (25.3)	116 (22.9)	111 (29.7)	171 (25.8)	54 (23.8)	68 (23.7)	0.178
Any other addiction treatment or services	191 (9.3)	42 (8.3)	40 (10.7)	56 (8.5)	21 (9.3)	32 (11.2)	0.518
Unable to access addiction treatment	302 (14.7)	74 (14.6)	47 (12.6)	92 (13.9)	39 (17.2)	50 (17.4)	0.341
Behavioral risk factors[a,b]							
Attacked, assaulted, or suffered violence	233 (11.3)	47 (9.3)	62 (16.6)	81 (12.2)	14 (6.2)	29 (10.1)	0.684
Drug dealing	299 (14.5)	61 (12.0)	74 (19.8)	118 (17.8)	16 (7.1)	30 (10.5)	< 0.001
Sex work involvement	505 (24.6)	144 (28.4)	75 (20.1)	166 (25.1)	51 (22.5)	69 (24.0)	0.060
Incarceration	283 (13.8)	76 (15.0)	51 (13.6)	93 (14.1)	27 (11.9)	36 (12.5)	0.786
Non-fatal overdose	272 (13.2)	77 (15.2)	54 (14.4)	84 (12.7)	28 (12.3)	29 (10.1)	0.291
Other factors							

(*Continues*)

Table 1. (Continued)

Characteristics	*Total n = 2057 (100%)*	*Persistent injection n = 507 (24.6%)*	*Persistent injection with late cessation n = 374 (18.2%)*	*Gradual cessation n = 662 (32.2%)*	*Early cessation with late relapse n = 227 (11.0%)*	*Early cessation n = 287 (14.0%)*	*P*
Ever been diagnosed with a mental health issue	740 (36.0)	179 (35.3)	167 (44.7)	233 (35.2)	65 (28.6)	96 (33.5)	0.001
Year of enrollment, median (quartile 1–quartile 3)	1999 (1996–2006)	1998 (1996–2006)	2006 (1996–2007)	2003 (1996–2007)	1996 (1996–2006)	1998 (1996–2006)	< 0.001
Study cohort designation (ACCESS)	370 (18.0)	65 (12.8)	98 (26.2)	143 (21.6)	21 (9.3)	43 (15.0)	< 0.001
Follow-up information							
Length of follow-up (months), median (quartile 1–quartile 3)	113.4 (63.4–161.7)	124.9 (50.6–211.6)	118.8 (73.0–149.5)	107.1 (58.1–135.5)	131.3 (96.6–211.3)	102.8 (57.2–138.9)	< 0.001
Number of deaths	495 (24.1)	126 (24.9)	73 (19.5)	180 (27.2)	50 (22.0)	66 (23.0)	0.071
Lost to follow-up	462 (22.5)	102 (20.1)	71 (19.0)	126 (19.0)	67 (29.5)	96 (33.4)	< 0.001

[a]Denotes behaviors and events in the previous 6 months, measured at baseline. [b]Frequency refers to the number of individuals who responded 'yes' to the measure.

in the 'persistent injection' group [adjusted odds ratio (AOR) = 1.02, 95% confidence interval (CI) = 1.00, 1.04] and the 'persistent injection with late cessation' group (AOR = 1.03, 95% CI = 1.01, 1.04). Further, not being in a stable relationship was positively associated with being in the 'persistent injection' group (AOR = 1.64, 95% CI = 1.18, 2.27), the 'persistent injection with late cessation' group (AOR = 1.59, 95% CI = 1.12, 2.27) and the 'gradual cessation' group (AOR = 1.44, 95% CI = 1.06, 1.97).

Baseline substance use factors, including at least daily heroin injection and binge injection drug use, were found to be predictive of long-term trajectories. Specifically, compared to the 'early cessation' group, participants who injected heroin daily were more likely to be in the 'persistent injection' group (AOR = 1.41, 95% CI = 1.03, 1.93) and the 'gradual cessation' group (AOR = 1.36, 95% CI = 1.01, 1.83). Moreover, participants who engaged in binge injection drug use at baseline were at 63% increased odds of being in the 'persistent injection' group (AOR = 1.63, 95% CI = 1.19, 2.22) and 77% increased odds of being in the 'gradual cessation' group (AOR = 1.77, 95% CI = 1.31, 2.40).

Sensitivity analysis results

In sensitivity analysis, the 462 participants who were lost to follow-up and the 495 participants who died were treated as dropouts at the time of their first missed study visit. When applying the Roy latent dropout pattern-mixture model we found a similar class membership distribution, with 489 (23.8%) participants in the 'persistent injection' group, 461 (22.4%) participants in the 'persistent injection with late cessation' group, 555 (27.0%) participants in the 'gradual cessation' group, 211 (10.2%) participants in the 'early cessation with late relapse' group and 341 (16.6%) participants in the 'early cessation' group. Results regarding class membership and the trajectory plot comparing to the standard GMM are presented in Supporting information, Table S6 and Fig. S1.

In the second sensitivity analysis, 974 participants were identified as having at least 10 years' follow-up time. Model fit statistics are presented in Supporting information, Table S7. As shown in Supporting information, Fig. S2, with a five-class solution, 433 (44.5%) participants injected drugs persistently over the study period, with 76 (7.8%) participants in the 'persistent injection' group and 357 (36.7%) participants in the 'persistent injection with late cessation' group. Overall, 541 (55.5%) participants demonstrated different cessation patterns. With the four-class solution, 502 (51.5%) participants showed relatively persistent injection trajectories, and 49.5% of the participants demonstrated early and delayed cessation patterns (figure not shown).

Table 2 Model comparison with an increasing number of trajectories.

Number of Classes	*1*	*2*	*3*	*4*	*5*	*6*
AIC	28 579.5	27 082.1	26 480.5	26 273.1	26 108.3	26 004.8
BIC	28 607.7	27 138.4	26 565.0	26 385.6	26 249.0	26 173.6
LMR LRT *P*-value		0.00	0.00	0.02	0.01	0.52
Entropy		0.446	0.455	0.446	0.440	0.411
Averaged posterior probability of group membership (range)		0.79–0.82	0.59–0.81	0.59–0.76	0.51–0.74	0.47–0.71
Sample size per class based on the estimated model (%, range)		45.8–54.2	26.7–41.7	11.9–36.1	13.4–28.0	11.4–22.2

AIC = Akaike information criterion. BIC = Bayesian information criterion. LMR LRT = Lo–Mendell–Rubin likelihood ratio test.

DISCUSSION

In the present study, we identified five distinct injection drug use trajectories among people who inject drugs in Vancouver, Canada. Given that almost half the study participants had injected drugs for 15 years at study enrollment, approximately one-quarter of the participants remained persistent injectors during the study period, and only a small portion of participants achieved sustained cessation by the end of the study period. These trajectories displayed associations with several individual characteristics and drug use behaviors measured at baseline.

Our findings regarding injection drug use trajectories are comparable to studies conducted in the United States [13,19] and the Netherlands [25], in which researchers also identified five trajectory groups. Further, our findings are consistent with previous findings indicating that the majority of participants experienced at least one cessation and relapse episode (either at early or late follow-up periods) during the study period. Specifically, three groups (i.e. 'early cessation', 'early cessation with late relapse', 'gradual cessation') demonstrated different rates of declining probability of injection. In the ALIVE cohort in the United States, although 31.9% of the participants were categorized as persistent injectors, their estimated probability of injection dropped below 50.0% at the end of the study period whereas, in our study, the estimated probability of injection for 24.6% of the participants remained above 65.0% during the study period. This difference could be potentially explained by distinct drug use patterns, cultural

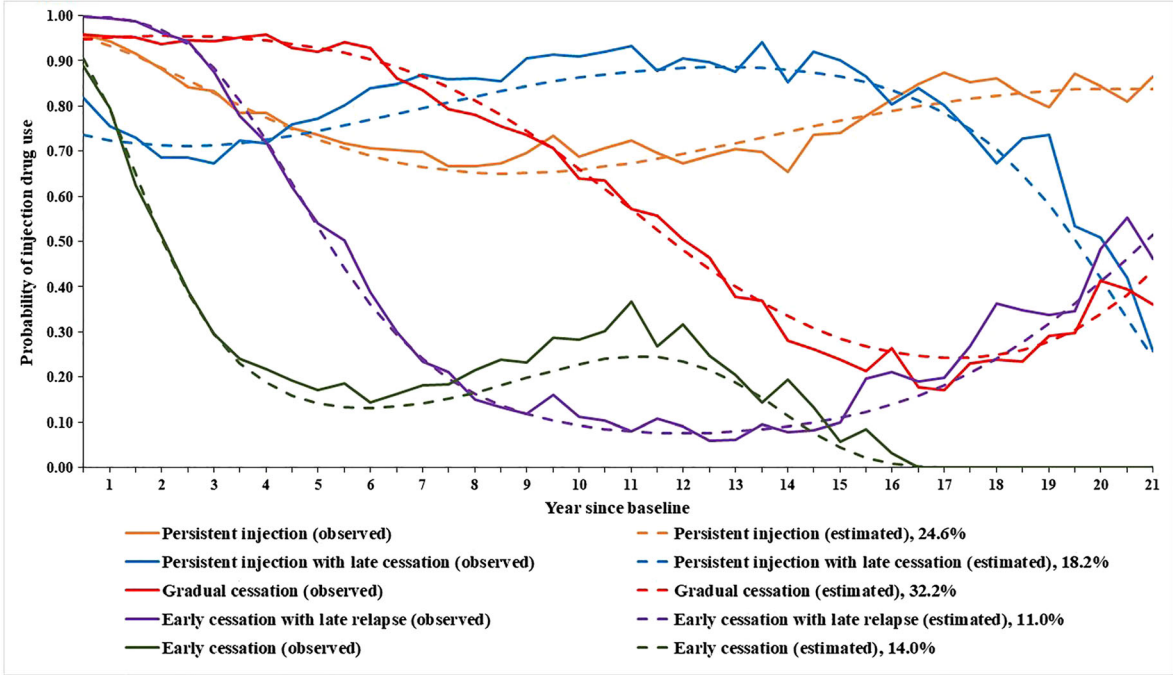

Figure 1 Injection drug use trajectory classes using growth mixture modeling among 2057 people who use injection drugs in Vancouver, British Columbia, Canada, 1996–2017. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 3 Bivariable multinomial logistic regression analyses of baseline demographic characteristics, drug use behaviors and social–structural exposures associated with different trajectory classes among 2057 people who use injection drugs, the Vancouver Injection Drug Users Study and AIDS Care Cohort to Evaluate Exposure to Survival Services, Vancouver, British Columbia, Canada, 1996–2017.

	Odds ratio (95% confidence interval), early cessation as the reference group							
Characteristics	*Persistent injection*	*P*	*Persistent injection with late cessation*	*P*	*Gradual cessation*	*P*	*Early cessation with late relapse*	*P*
Socio-demographic factors								
Younger age, per year	1.02 (1.00, 1.03)	0.019	1.00 (0.99, 1.02)	0.640	1.00 (0.99, 1.02)	0.577	1.00 (0.99, 1.02)	0.563
Male	0.85 (0.63, 1.14)	0.271	1.29 (0.94, 1.79)	0.119	1.15 (0.86, 1.53)	0.346	1.07 (0.74, 1.53)	0.725
White ethnicity	1.08 (0.81, 1.45)	0.595	1.07 (0.78, 1.46)	0.675	1.16 (0.87, 1.53)	0.309	1.53 (1.07, 2.19)	0.020
High school completion or higher	0.79 (0.57, 1.09)	0.146	0.65 (0.46, 0.91)	0.011	0.63 (0.46, 0.85)	0.003	1.25 (0.83, 1.89)	0.284
Not being in a stable relationship[a]	1.56 (1.14, 2.15)	0.006	1.59 (1.13, 2.24)	0.007	1.43 (1.06, 1.93)	0.019	1.12 (0.77, 1.63)	0.542
Employment status (regular/temporary job; self-employed)[a]	0.92 (0.63, 1.33)	0.643	1.05 (0.71, 1.56)	0.799	1.22 (0.86, 1.73)	0.274	1.12 (0.72, 1.74)	0.608
Unstable housing	1.12 (0.82, 1.54)	0.477	1.35 (0.96, 1.91)	0.086	1.09 (0.81, 1.48)	0.576	0.83 (0.58, 1.21)	0.333
Substance use[a]								
Daily heroin injection	1.46 (1.09, 1.97)	0.013	0.95 (0.69, 1.31)	0.741	1.31 (0.98, 1.74)	0.067	1.06 (0.74, 1.53)	0.747
Daily stimulant injection	1.42 (1.03, 1.94)	0.030	0.88 (0.63, 1.25)	0.481	1.32 (0.97, 1.78)	0.075	1.58 (1.09, 2.28)	0.016
Daily speedball injection	1.56 (1.00, 2.42)	0.051	0.80 (0.48, 1.34)	0.402	1.14 (0.73, 1.77)	0.569	1.07 (0.62, 1.86)	0.815
Daily prescription opioid injection	0.67 (0.29, 1.58)	0.361	1.57 (0.72, 3.40)	0.258	1.27 (0.61, 2.64)	0.524	0.88 (0.33, 2.35)	0.800
Daily non-injection crack cocaine use	1.00 (0.70, 1.41)	0.985	1.66 (1.16, 2.37)	0.005	1.20 (0.86, 1.67)	0.275	0.70 (0.45, 1.10)	0.120
Daily cannabis use	0.93 (0.64, 1.34)	0.695	1.25 (0.86, 1.83)	0.246	0.84 (0.59, 1.20)	0.337	1.02 (0.66, 1.58)	0.930
Daily alcohol use	0.84 (0.58, 1.21)	0.338	0.65 (0.43, 0.98)	0.039	0.88 (0.62, 1.24)	0.450	1.02 (0.66, 1.56)	0.947
Binge injection drug use	1.59 (1.18, 2.15)	0.003	1.07 (0.77, 1.48)	0.689	1.62 (1.21, 2.16)	0.001	1.37 (0.96, 1.97)	0.085
Years since injection drug use	0.99 (0.98, 1.01)	0.236	1.01 (0.99, 1.02)	0.523	1.00 (0.99, 1.02)	0.802	1.00 (0.99, 1.02)	0.893
Treatment experience[a]								
Opioid agonist therapy	0.95 (0.68, 1.34)	0.785	1.36 (0.96, 1.94)	0.084	1.12 (0.81, 1.55)	0.496	1.00 (0.67, 1.51)	0.997
Any other addiction treatment or services	0.72 (0.44, 1.17)	0.181	0.95 (0.58, 1.56)	0.850	0.74 (0.47, 1.16)	0.187	0.81 (0.45, 1.45)	0.474
Unable to access addiction treatment	0.81 (0.55, 1.20)	0.288	0.68 (0.44, 1.05)	0.081	0.76 (0.52, 1.11)	0.159	0.98 (0.62, 1.55)	0.929
Behavioral risk factors[a]								
Attacked, assaulted, or suffered violence	0.88 (0.51, 1.52)	0.645	1.04 (0.62, 1.76)	0.886	0.80 (0.48, 1.32)	0.377	0.77 (0.37, 1.61)	0.485
Drug dealing	1.17 (0.74, 1.86)	0.503	2.11 (1.34, 3.33)	0.001	1.86 (1.21, 2.85)	0.005	0.65 (0.35, 1.22)	0.182
Sex work involvement	1.26 (0.90, 1.76)	0.173	0.79 (0.55, 1.15)	0.219	1.06 (0.77, 1.47)	0.707	0.92 (0.61, 1.38)	0.675
Incarceration	1.23 (0.80, 1.88)	0.342	1.10 (0.70, 1.74)	0.681	1.14 (0.76, 1.72)	0.529	0.94 (0.55, 1.60)	0.824
Non-fatal overdose	1.60 (1.01, 2.51)	0.044	1.51 (0.93, 2.43)	0.095	1.30 (0.83, 2.03)	0.254	1.26 (0.73, 2.18)	0.415
Other factors								
Ever been diagnosed with a mental health issue	1.08 (0.80, 1.47)	0.621	1.61 (1.17, 2.21)	0.004	1.08 (0.81, 1.45)	0.596	0.80 (0.55, 1.17)	0.246
Year of enrollment	1.01 (0.98, 1.04)	0.483	1.07 (1.04, 1.10)	< 0.001	1.04 (1.02, 1.07)	< 0.001	0.95 (0.92, 0.98)	0.001
Study cohort designation (ACCESS)	0.83 (0.55, 1.27)	0.394	2.02 (1.35, 3.00)	< 0.001	1.56 (1.08, 2.27)	0.019	0.58 (0.33, 1.01)	0.053

[a]Denotes behaviors and events in the previous 6 months, measured at baseline.

Table 4 Multivariable multinomial logistic regression analyses of baseline demographic characteristics, drug use behaviors, and social–structural exposures associated with different trajectory classes among 2057 people who use injection drugs, the Vancouver Injection Drug Users Study and AIDS Care Cohort to Evaluate Exposure to Survival Services, Vancouver, British Columbia, Canada, 1996–2017.

	Adjusted odds ratio (95% confidence interval)									
Characteristics	*Persistent injection versus early cessation*	*P*	*Persistent injection with late cessation versus early cessation*	*P*	*Gradual cessation versus early cessation*	*P*	*Early decrease with late relapse versus early cessation*	*P*	*Persistent injection versus early decrease with late relapse*	*P*
Younger age, per year	1.02 (1.00, 1.04)	0.041	1.03 (1.01, 1.04)	0.007	1.01 (1.00, 1.03)	0.133	1.00 (0.98, 1.02)	0.847	1.02 (1.00, 1.04)	0.036
Male	0.86 (0.63, 1.18)	0.358	1.28 (0.91, 1.81)	0.162	1.19 (0.87, 1.62)	0.278	1.10 (0.75, 1.61)	0.635	0.79 (0.55, 1.11)	0.172
Not being in a stable relationship[a]	1.64 (1.18, 2.27)	0.003	1.59 (1.12, 2.27)	0.010	1.44 (1.06, 1.97)	0.020	1.12 (0.76, 1.64)	0.566	1.46 (1.02, 2.09)	0.038
Daily heroin injection[a]	1.41 (1.03, 1.93)	0.030	1.01 (0.72, 1.42)	0.949	1.36 (1.01, 1.83)	0.046	1.01 (0.70, 1.47)	0.956	1.40 (1.00, 1.95)	0.051
Binge injection drug use[a]	1.63 (1.19, 2.22)	0.002	1.26 (0.90, 1.77)	0.183	1.77 (1.31, 2.40)	< 0.001	1.23 (0.85, 1.78)	0.277	1.32 (0.95, 1.84)	0.096
Year of enrollment	1.03 (1.00, 1.06)	0.061	1.08 (1.05, 1.12)	< 0.001	1.06 (1.03, 1.09)	< 0.001	0.95 (0.92, 0.99)	0.006	1.08 (1.05, 1.12)	< 0.001
	Adjusted odds ratio (95% confidence interval)									
Characteristics	*Persistent injection with late cessation versus early decrease with late relapse*	*P*	*Gradual cessation versus early decrease with late relapse*	*P*	*Persistent injection versus gradual cessation*	*P*	*Persistent injection with late cessation versus gradual cessation*	*P*	*Persistent injection versus persistent injection with late cessation*	*P*
Younger age, per year	1.03 (1.01, 1.05)	0.007	1.02 (1.00, 1.03)	0.112	1.01 (0.99, 1.02)	0.451	1.01 (1.00, 1.03)	0.100	0.99 (0.98, 1.01)	0.366
Male	1.17 (0.80, 1.70)	0.421	1.08 (0.77, 1.52)	0.653	0.73 (0.56, 0.94)	0.015	1.08 (0.81, 1.44)	0.608	0.67 (0.50, 0.91)	0.010
Not being in a stable relationship[a]	1.42 (0.97, 2.09)	0.071	1.29 (0.92, 1.82)	0.146	1.13 (0.86, 1.49)	0.375	1.10 (0.81, 1.49)	0.528	1.03 (0.74, 1.42)	0.871
Daily heroin injection[a]	1.00 (0.70, 1.44)	0.998	1.34 (0.97, 1.86)	0.075	1.04 (0.81, 1.33)	0.761	0.75 (0.56, 0.98)	0.037	1.40 (1.04, 1.87)	0.025
Binge injection drug use[a]	1.02 (0.72, 1.46)	0.895	1.44 (1.05, 1.99)	0.025	0.92 (0.72, 1.17)	0.480	0.71 (0.54, 0.93)	0.014	1.29 (0.97, 1.72)	0.081
Year of enrollment	1.14 (1.10, 1.18)	< 0.001	1.12 (1.08, 1.15)	< 0.001	0.97 (0.95, 0.99)	0.004	1.02 (1.00, 1.05)	0.064	0.95 (0.92, 0.97)	< 0.001

[a]Denotes behaviors and events in the previous 6 months, measured at baseline.

settings or other social–structural conditions operating in the study sites.

The first sensitivity analysis took into account potential non-ignorable dropout. The trajectory shapes as well as the interpretation of the latent classes were in line with the primary findings. Overall, for the Roy model, 46.2% of participants showed relatively persistent injection trajectories (i.e. the 'persistent injection' and 'persistent injection with late cessation' groups) over time, which was higher than the main result of 42.8%. Therefore, the Roy model indicated a slightly worse assessment of the injection drug use trajectories among the sample compared to the primary findings. In the second sensitivity analysis, the result was consistent with the primary findings in that more than half the entire sample showed a decreasing trend of injection drug use over time. However, with the restriction on longer follow-up time, the decreasing rate of injection drug use among the 'early cessation' group was much slower. For example, in primary analysis, the estimated probability of injection drug use dropped below 30% around the third year, whereas in sensitivity analysis, it was around the 6th year of follow-up. We also observed increased proportions for the 'persistent injection with late cessation', 'early cessation' and 'delayed cessation' groups. In the primary analysis, the estimated probability of injection drug use for the 'gradual cessation' group appeared to increase slightly from approximately 25 to 40% at the end of the 3 years of follow-up. This small increase did not indicate a clear relapsing pattern. Further, we did not observe such an increase in the 'gradual cessation' group in the second sensitivity analysis with the restriction on longer follow-up time. Therefore, it is possible that the inflation was due to the small proportion of participants retained at the end of the study or a potential misclassification bias with the 'early cessation with late relapse' group.

We observed that both age and year of study enrollment were associated with different injection trajectories. Compared to the 'early cessation' group, participants of younger age were at higher risk of engaging in persistent injection patterns (i.e. 'persistent injection' and 'persistent injection with late cessation'). This is consistent with the finding that older age was associated with 6-month injection cessation in previous studies utilizing ACCESS and VIDUS cohorts [6,40]. Studies in other settings also demonstrated that older age increased the likelihood of experiencing long-term cessation and decreased the risk of relapse [8,41]. Compared to the 'persistent injection' group, participants enrolled in more recent years were more likely to be in the 'persistent injection with late cessation' and 'gradual cessation' groups. It is possible that these findings are reflective of the continuing implementation and expansion of various harm reduction strategies in Canada. For instance, beginning in 2000, efforts have been made to transform the centralized syringe exchange program to a decentralized, multi-site syringe distribution program [42]. One study demonstrated a significant increase in the proportion of people in Vancouver reporting a 6-month injection drug use cessation during the needle and syringe expansion period [7]. In 2003, North America's first legal supervised injection site opened in Vancouver. Studies have indicated the potential role of supervised injecting facility in promoting the uptake of addiction treatment and increasing the likelihood of 6-month injection cessation [9]. Together, these findings suggest that the age of participants and year of enrollment may be predictive of both short- and long-term injection behavioral change, and indicate potential cohort and period effects.

Being in a stable relationship at baseline was positively associated with being in the 'early cessation' group, suggesting that being married or having a close relationship is associated with a better long-term drug use outcome. It is possible that individuals in stable relationships may enjoy greater social support, which may serve to mitigate stress and thereby reduce the use of illicit drugs. This finding is further supported by an extensive literature examining relationship status and substance use patterns [43–45].

Binge injection drug use at baseline was associated with an increased likelihood of being in the 'persistent injection' and 'gradual cessation' groups. This finding is consistent with observations made in other studies that high intensity injecting not only impedes injection cessation, but is also negatively associated with sustained injection cessation [5,7,8,19,46]. We also found that drug of choice appears to have an impact on long-term drug use trajectories. Various types of substance use were associated with injection trajectories in bivariable analyses. However, only daily heroin injection remained positively associated with being in the 'persistent injection' and 'gradual cessation' groups in the multivariable model. Studies have shown that polydrug use is associated with change in injecting behavior [12,19,25]. In the current study, speedball injection was only marginally associated with 'persistent injection' in bivariable analyses, which provided limited information to help differentiate long-term drug use trajectories. Future studies investigating the relationship between early poly substance use (e.g. cumulative number of types of substances reported) and later trajectories would potentially be of benefit.

Baseline exposures were examined in our study in order to identify predictors of trajectory group membership. However, we recognize that injection behavior could change under the influence of important events or cumulative exposure to these events over time. Therefore, there is a need for future study to more closely examine how these exposures, as time-varying covariates, would influence the shape of injection trajectories.

Limitations in the current study need to be considered. First, the use of self-report, especially for socially

stigmatized and criminalized behaviors (e.g. illicit substance use), could introduce errors of recall and social-desirability bias. Secondly, the dichotomous variable of self-reported injection drug use (yes versus no) was used for GMM, therefore the identified trajectory classes could not differentiate between variability in frequency and quantity of injection drug use. Thirdly, there could be potentially important baseline characteristics that were not included when predicting trajectory groups. For example, we were not able to include tobacco smoking as the information was not routinely measured in the survey questionnaires. Fourthly, this study is not based on a random sample of people who inject drugs and is conducted in BC, Canada, where the social–structural conditions (e.g. harm reduction strategies, attitudes towards injection drug use) could be different compared to other settings. Therefore, these factors may limit the generalizability of the findings. Further, to explore the predictive factors for distinct drug use trajectories, we used the three-step method due to the practical reason that we had a large number of covariates and the recognized disadvantages of joint model estimation approach for our research purpose [36]. However, we recognize that this approach does not account for potential classification errors, although modified three-step approaches by Wang *et al* [47] and Vermunt [48] make allowances for issues such as errors in classification and bias adjustment.

Recent concerns have been noted regarding the validity of GMM analysis due to the 'cat's cradle' effect, which is a strong tendency to identify four prototypical classes in substance use research: stable high use, stable low use, increasing use and decreasing use [49]. However, it is notable that in the current study, two relatively persistent injection trajectories and three different levels of decreasing trajectories were found. Furthermore, the 'fling' trajectories (i.e. 'persistent injection with late cessation', 'early cessation with late relapse') were also identified. Together, these more interesting trajectories deviate from the prototypical classes, which suggest that the current study may be less susceptible to the cat's cradle effect.

Finally, with the reported entropy value and the averaged posterior probability of group membership, there could be classification bias introduced when assigning classes. However, it is worth mentioning that entropy is not an ideal measure of model fit, nor should be solely used to select the number of latent classes [50]. Entropy value could be negatively influenced by chance misclassification when having a higher number of classes [51], be sensitive to the patterns of growth in each class [52] and potentially depend on the context and the variables used in the study [53,54]. Even with this classification uncertainty, summarizing 20 years' follow-up data at individual level in relation to several injection drug use trajectories has proven useful. Further, the primary findings were consistent with studies from other settings [13,19,25]. Several factors were found to be predictive of these trajectory classes, which further indicate that the identified trajectory classes were different from each other. Further, the 462 participants who were lost to follow-up and 495 who participants died were treated as dropouts during the study period, which might also introduce bias regarding group classification. To account for attrition, our primary findings from GMM were based on maximum-likelihood estimation, which utilized all the available data to generate parameter estimates. In both sensitivity analyses, the distribution of the trajectory class membership was consistent with the primary research findings that more than half the sample demonstrated different cessation patterns. Recent developments offer a variety of more sophisticated methodologies (e.g. Muthén–Roy pattern-mixture model, Diggle–Kenward model) to understand missing data mechanisms in growth mixture modeling framework [38].

CONCLUSIONS

The current study took advantage of more than 20 years of rich information from over 2000 individuals by creating a unique cohort combining ACCESS and VIDUS, which are among the longest-standing community-recruited cohort studies of people who inject drugs in the world. The study identified the existence of five distinct injection drug use trajectories among people who use drugs in Vancouver, Canada. Despite the fact that at recruitment many participants have already been injecting drugs for some 5–25 years, approximately three-quarters of them reduced the frequency of injection drug use at the end of the study period, and this estimate might be taken as an encouraging sign. This study represents a relatively comprehensive investigation of individual, social and structural factors for different trajectories of injection drug use throughout long-term periods. The findings from this study further highlight the importance of identifying targeted interventions for long-term injection drug use and the need to identify factors that support cessation and protect against relapse.

Declaration of interests

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Prevalence and the averaged posterior probability of group membership for the five-class solution.

Table S2 Bivariable multinomial logistic regression analyses of baseline demographic characteristics, drug use behaviours, and social-structural exposures associated with

different trajectory classes, using persistent injection as the reference group.

Table S3 Bivariable multinomial logistic regression analyses of baseline demographic characteristics, drug use behaviours, and social-structural exposures associated with different trajectory classes, using persistent injection with late cessation as the reference group.

Table S4 Bivariable multinomial logistic regression analyses of baseline demographic characteristics, drug use behaviours, and social-structural exposures associated with different trajectory classes, using gradual cessation as the reference group.

Table S5 Bivariable multinomial logistic regression analyses of baseline demographic characteristics, drug use behaviours, and social-structural exposures associated with different trajectory classes, using early cessation with late relapse as the reference group.

Table S6 Sensitivity analysis 1: comparison of class membership between standard growth mixture modeling and Roy latent dropout pattern-mixture modeling.

Table S7 Sensitivity analysis 2: comparison with an increasing number of trajectories.

Figure S1 Sensitivity analysis 1: injection drug use trajectory classes using standard growth mixture modeling and Roy latent dropout pattern-mixture modeling.

Figure S2 Sensitivity analysis 2: injection drug use trajectory classes among 974 people with at least ten years follow-up time.