Original Article

Title

Trajectories of injecting behavior in the Amsterdam Cohort Study among Drug Users

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Abstract

Background:

Injecting frequency among people who inject drugs (IDU) can change along distinct trajectories, which can reflect on incidence of HIV and HCV infections. We aimed at assessing these patterns of longitudinal changes, their predictors and their association with the incidence of HIV and HCV.

Methods:

We analyzed data from the Amsterdam Cohort Study among Drug Users, selecting participants recruited 1985-2005, injecting drugs before cohort entry and with records in at least three different six months intervals (N=740). We used latent class mixed models to identify distinct trajectories of injecting, multinomial regression to identify socio-demographic variables associated with those patterns and Kaplan-Meier analysis for the estimation of the corresponding cumulative HIV and HCV incidence.

Results:

Five distinct patterns for injecting frequency and for injecting since last visit were identified. Majority of participants (three groups, 69% of participants) had stable risk injecting behavior; the remaining displayed a decrease in injecting over time. Those with longer duration of injecting at cohort entry and those who entered the cohort in earlier years tended to have continuing high risk behavior. The HIV risk was highest among those with continuing high risk behavior and its changes over time mirrored the patterns of change in injecting in a group with decrease in injecting.

Conclusions:

Individual longitudinal patterns of changes in injecting behavior are related to socio-demographic and drug use variables and are reflected in the incidence of HIV infections. Understanding these associations might provide valuable information for targeted interventions.

Keywords:

Finite mixture models – behavioral change – injecting drug use

1. Introduction

Injecting drug users (IDU) may change their risk behavior in the course of their injecting career, either under the influence of harm reduction programs or for other reasons . Such changes will affect the risk of infectious diseases such as HIV and HCV, depending for example on frequency of infecting and sharing of syringes and needles . Young and recent onset injectors often display high levels of risk behavior and therefore put themselves at increased risk of contracting a blood borne infection, while older and more experienced injectors may present lower levels of risk behavior .

Longitudinal changes in behavior can be conceptualized as trajectories describing typical patterns of change during the injecting career. Ideally, one would like to predict the development of risk behavior over time from individual characteristics. Consequently, characterizing individuals in terms of typical behavioral trajectories and predicting the future development might provide valuable information for targeting interventions. The analysis to identify the corresponding patterns can be conducted using semi-parametric latent class growth modeling or finite mixture models . This methodology was applied in multiple research areas and distinct trajectories were described in relation to alcohol use , smoking , drug use in general and joint use of multiple drugs , and aggression, delinquency or social withdrawal .

Three studies addressed patterns of longitudinal changes in injecting over time using US samples of drug users . Xie et al. found four different patterns of remission (varying between treatment resistance and different levels of improvement) in a sample from the New Hampshire Dual Disorders study. Hser et al. used a two component modelling (use versus non-use and frequency of use among the users) and identified three trajectories of injecting frequency among narcotic addicts originally admitted to the California Civil Addict Program. In a more recent publication, Genberg et al. analyzed data from the ALIVE study in Baltimore and described five patterns of drug use cessation. All these studies demonstrated similar patterns among drug users in the USA, despite different samples and variation in analytical methods. However, patterns of change in injecting can depend on cultural settings, and it is not clear if the findings can be generalized to other populations. Further evidence from other countries is necessary to confirm existing observations. A study from Switzerland reported trajectories of drug use behavior over time, but using only two predefined categories: a difference between the first and last visit, and assuming constant behavior during all visits . Previous research also did not study associations between patterns of changes in injecting and the risk of attracting related infections which is the important public health outcome of injecting.

In order to assess patterns of changes in injecting frequency among IDU in a European population, we used data from the Amsterdam Cohort Study among Drug Users (ACS). We studied potential heterogeneity in patterns of

change, and assessed how the different patterns of change were linked to individual characteristics of the participants, and whether they were associated with the incidence of HIV and HCV.

2. Methods

2.1. Data source

The ACS has been described extensively elsewhere . In brief, it is an open, prospective cohort study initiated to investigate the prevalence, incidence and risk factors of infections with HIV-1 and other blood borne and/or sexually transmitted infections, as well as the effects of interventions. Participants are invited to visit the Amsterdam Health Service every 4–6 months. At study entry and every visit, they give blood for HIV testing and storage; they also complete a standardized questionnaire about their health, drug use and sexual risk behavior, and socio-demographic situation. Participation in the ACS is voluntary, and written informed consent is obtained prior to data collection. The study was approved by the institutional review board of the Academic Medical Center in Amsterdam.

We initially included data of 1,175 IDU, who were recruited between April 1985 and November 2005 and had ever injected ('ever injectors') at cohort entry. However, for the analysis of pattern of change in injecting, we restricted the sample to 740 IDU with visits in at least three separate six-month time windows during the first 10 years since cohort entry. The dataset contained information on sex, age at cohort entry and age at first injection, needle sharing (ever) at cohort entry, the frequency of current injecting (in the last six months or since last visit) using eight categories: no injection, less than 1 day/month, 1 day/month, 2-3 days/month, once weekly, 2-6 days/week, once daily, and several times daily, and type of drugs preferentially used in last six months.

2.2. Statistical analysis

First, we described the sample in terms of socio-demographic variables, prevalence of HIV and HCV and drug use at study entry. Second, we assessed which time scale has the strongest association with injecting frequency: duration of injecting (which would indicate that the natural history of injecting is most important), year of entry in the cohort (indicating secular changes in the population of IDU) or time in the cohort (effects of participation in the cohort on behavior). In order to remove effects of drop out or differential censoring due to death, this analysis was restricted to a subsample of participants who had information about frequency of injecting in the time window of 4.5-5.5 years in the cohort (N=542). Initially, the original frequency of injecting variable was used and the results were visually inspected. For a formal analysis, frequency of injecting was dichotomized in different ways and in each case random effects logistic regression was used for analysis. In these models duration of injecting at cohort entry, year of entry in the cohort and time in the cohort were included as

independent variables and dichotomized frequency of injecting at cohort entry and after five years as dependent variable, linked by participants` ID as random effects to link behavior at these two time points. This analysis was conducted with SAS macro %glimmix . In further analysis, time variable with the strongest effect (based on odds ratio) was used. Third, we used a growth mixture model to identify different patterns of changes in injecting behavior during the cohort time. Mixture models combine the features of longitudinal analysis and cluster analysis: groups with different average patterns of frequency of injecting over time are identified and their trajectories of changes in the frequency of injecting are described. The trajectories are described by polynomial functions and subjects are classified as belonging to a given group based on a summary measure describing deviation from the average trajectory for the group . The individual group membership is not fixed, but is estimated based on the highest probability of belonging to the given group. While the earlier versions of mixture models (latent class analysis models) did not allow for variation within groups, growth mixture models combine features of mixed and mixture models . In each run the number of distinct groups has to be specified, but the results for different numbers of groups can be compared by statistical criteria such as the Bayesian Information Criterion (BIC or adjusted BIC) . In typical applications with large datasets, even for a high number of groups there are significant improvements in BIC. Therefore, the decision about the number of groups should also consider the interpretation of the distinct groups. For information about quality of separation of the different classes we present posterior class membership probabilities and report the relative entropy measure . Since the outcome variable (frequency of injecting) was ordinal and the data points at which it was assessed were not evenly distributed, we used for the analysis the lcmm library in R . Fourth, we studied whether socio-demographic characteristics, HIV and HCV status and history of drug use at cohort entry can be used to predict the estimated group membership with regard to the trajectories applying chi-squared test for univariate and multinomial regression for multivariable analysis. Finally, we applied Kaplan-Meier life table analysis to assess the cumulative incidence of HCV and HIV infection since cohort entry for groups with different behavior as defined in the mixture model analysis.

3. **Results**

3.1. General characteristics and injecting frequency

About 64% of the 740 study participants in the final sample were males, 26% were HIV-positive and 85.5% HCV-positive at cohort entry (among the 676 cases with known HCV status). Median age at cohort entry was 31.0 years (interquartile range (IQR): 27.2-36.1), and median duration of injecting at cohort entry was 8.6 years (IQR: 3.8-13.9). At cohort entry, 25.6% of the participants had not injected drugs in the last six months, 30.2% were injecting less than once per month, 5.0% were injecting once per month, 30.0% were injecting on 2-3 days

per month, 5.0% were injecting once weekly to once daily and 4.1% were injecting several times daily. For those who injected drugs in the last six months, in 54.8% cocaine and heroin were the injection drugs of choice in the last six months, in 17.2% heroin only, in 12.5% cocaine only, in 6.9.% amphetamine, in 4.0% methadone and in 4.5% the drug of choice was unknown. Among those 370 IDU who provided the related information at cohort entry, 65% had ever shared syringes. 52.2% of the total sample entered the cohort before 1990, 31.4% between 1990 and 1995 and the remaining 17.4% thereafter. Due to frequent drop outs over the first 10 years after cohort entry, the sample decreased in approximately linear fashion to about 44% of the initial sample size.

3.2. Importance of different time variables for the change in frequency of injecting over time

In the subsample of 542 IDUs for whom information between 4.5 and 5.5 years in the cohort was available, the likelihood of more frequent injecting increased with the duration of injecting before cohort entry, but decreased with the more recent year of recruitment for the cohort and over the time in the cohort (Table 1). Based on the odds ratios, the effect of time in the cohort was about twice as large as the effect of year of recruitment; this was similar for other dichotomizations (data not shown). Therefore, the time in the cohort was chosen as time scale for the further analysis.

3.3. Patterns of change in injecting frequency over the time in the cohort

The analysis of trajectories describing the frequency of injecting suggested the existence of several distinct patterns. There was neither optimum in BIC nor in adjusted BIC up to seven groups (Table 2). Based on the interpretability and previous research a five-group solution was chosen, this solution displayed adequate separation of groups with posterior probabilities between 88.6% and 97.0% and a high entropy value of 0.87 for ordinal frequency of injecting and posterior probabilities between 84.0% and 94.6% and entropy of 0.82 for dichotomized frequency of injecting. Figure 1a) illustrates the average injecting frequency in each group over time, with horizontal lines indicating thresholds between categories of the original question. Figure 1b) displays the full distribution of the frequency of injecting over time in each of the groups. In three groups frequency of injecting was approximately stable over time: *rare to no injecting* (group 4: n=169, 22.8%), *constant daily or several times daily injecting* (group 1, n=112, 15.1%) and *variable injecting* (group 5: n=137, 18.5%). Two trajectories displayed a downwards trend – a slow downwards trend in *every 2nd day and less frequent injecting* (group 3: n=233, 31.5%) and a faster trend in the *decrease in injecting* (group 2: n=89, 12%) which ended in nearly no injecting after 6 years.

Similar different patterns were found for the probability of having injected since the last visit (Figure 2 a and b). In three groups, the probability of injecting did not change much over time. One group (*low probability of*

injecting, group 5: n=156, 21.1%) started with a low probability of injecting and over time the probability slightly decreased further. Another group oscillated around a 50% probability of injecting (*stopping and starting*, group 4, n=112, 15.1%). The largest group (*high probability of injecting*, group 2: n=286, 38.6%) had a constant probability of having injecting close to 100%. Two groups displayed patterns of strong decrease in the probability of injecting over the time in the cohort (*early decrease*, group 3: n=95, 12.9% and *late decrease*, goup 1: n=91, 12.3%).

Joint analysis of frequency of injecting and injecting since last visit provided further insights. Among those with *rare to no injecting* the largest was the group with *low probability of injecting* (Table 3). On the other hand, most of those with *constant daily or several times daily injecting* were also in the group with *high probability of injecting*. The group with *decrease in frequency of injecting* over time consisted of IDU with *early* and *late decrease* and with *high probability of injecting*. As could be expected, the group with *variable injecting* was mostly in the group of *starting and stopping*.

3.4. Patterns of change in injecting and socio-demographic characteristics or the risk of HIV and HCV

While several point estimates differed from 1, most of the association between patterns of change in injecting frequency and socio-demographic or behavioral characteristics lacked significance (Table 4). Longer duration of injecting before cohort entry decreased the probability of belonging to the groups with *no or rare injecting* and *decrease in injecting*. More recent year of cohort entry was associated with a higher probability of *no or rare injecting* and *variable injecting*. The findings for injecting since the last visit were similar (data not shown).

Across the patterns of change in injecting, there were differences with respect to the HIV free survival (Table 5). The HIV incidence was lowest in the group with *rare to no injecting*, followed by *decrease in injecting* group.in which all infections occurred during the reduction phase and before the no-injection state was reached (data not shown). In groups with continuing high exposure the incidence was higher. Since the analysis of incident cases was restricted to those who were negative at the cohort entry, the sample was too small to generate meaningful estimates for HCV incidence.

4. **Discussion**

The purpose of this study was to assess the association of longitudinal patterns in injecting behavior and socio-demographic data and their relationship with the risk of HIV and HCV infection. Based on the ACS data, we identified five patterns of change in injecting frequency over time in the cohort. These patterns displayed associations with socio-demographic variables on the one side and with the incidence of HIV on the other side.

The existence of distinct trajectories can be related to manifest and measurable variables such as economic status, gender or education, exposure to interventions, or latent variables, i.e. unknown or unmeasured characteristics (personality, personal experiences etc.). Discrete patterns rather than a continuum can result from categorical characteristics on the one side, but also from inherent dynamics of behavior on the other. In the case of injecting, specific patterns of change may exist in groups of friends, amongst those jointly participating in methadone programs or other activities targeting risk reduction among drug users. The existence of patterns of change can have implications for risk reduction programs, for example stable patterns of continuing risk exposure support programs minimizing risk of HIV. Patterns of variable injecting / stopping and starting the need of supportive interventions reducing risk behavior and finally risk decrease patterns indicate possibly effective interventions.

The variables with strongest association with patterns of change in injecting over time were duration of injecting at cohort entry and year of cohort entry. Effects of duration of injecting at cohort entry suggest specific natural history of injecting. In contrast, effects of year of cohort entry can be related to differences between cohorts (cohort effects) or changes in the environment (period effects). The dominating pattern was a stable frequency of injecting with only a marginal decrease over time. This is consistent with an earlier analysis of ACS data demonstrating that the transition to abstinence occurred rarely . However, there were groups which displayed a reduction in injecting over the time in the cohort. Most interesting is the pattern of a strong decrease in the frequency of injecting during the first three years in the cohort. Although it has to be kept in mind that this group was particularly small (only 12%), if future research could demonstrate the reasons behind the observed reduction, this could possibly be used to design more effective intervention strategies.

Our findings on trajectories of change in injecting agreed well with observations from IDU cohorts in the USA. For example, in the study by Xie et al. three of four groups displayed stable probability of substance use: close to zero (22.5%), close to 50% (21.4%) and close to 100% (25.2%), similar to our findings. The fourth group (31% of the sample) displayed a change from 100% to 0% over the period of 10 years. While we identified two trajectories of decrease – an early and late – the sum of these subgroups was 43.5%, very similar to the decrease trajectory found by Xie et al. . Also the remaining fractions were similar. Hser et al. identified three trajectories of injecting frequency: 1) consistent high level of use, 2) late decelerated group, among whom a subgroup of non-users was increasing after 10 years since initiation of use and those not quitting continued frequent use, and 3) “early quitters” who decreased their use within three years. The participants in this analysis were contacted only three times and data was constructed from retrospective interviews, which is different from our prospective cohort approach with regular follow-up. However, also in our analysis the pattern of reduction in injecting

frequency resulted from both: reduction in frequency of injecting among those who continued injecting and increase in the fraction of those who stopped injecting. Also the five trajectories for probability of injecting described by Genberg et al. displayed a very similar picture to ours and the percentages within each group were similar to our results. In general, the agreements between our findings from the Netherlands and previous studies from the USA point towards possible universality of observed patterns despite cultural differences and different organization of efforts to reduce burden of injecting drug use.

An interesting aspect is the question whether and how participation in the observational study affects the behavior with regard to injecting. Initially, we conceptualized the analysis as an assessment of the natural history of injecting among drug users, under the premise that ACS is mainly observational. In such a case, the main time variable for changes should be the individual duration of injecting. During the analysis, it became increasingly clear that entry into the cohort marked a special point, at least for part of the participants. This could be due to the contact with harm reduction services that influence injecting, e.g. methadone treatment.

Obviously, a lower frequency of injecting is associated with a lower risk for HIV – this is also likely to be the case, when frequency of injecting is decreasing over time, as confirmed in our analysis, but the numbers are too small to allow detailed interpretation.

4.1 Limitations

There are several limitations. First, our IDU population might not be representative, and the patterns of change might not be generalizable to other populations of IDU. Second, self-reported risk behavior can be subject to social expectation bias. If the strength of this bias evolved over time in cohort due to repeated contact with the service providers involved in the interviews, then this could be the cause of decrease in injecting frequency rather than a “true” risk reduction. However, it was previously demonstrated that drug users are able to give valid self-reports in the ACS where social desirability does not play a role since no illegal or embarrassing situation is involved and there are no sanctions .

There are also some limitations related to the statistical methods. While the three degree polynomials provide substantial flexibility, it might not be the best choice for the described process. If a subject changes frequently between high and low frequency of injecting within short time periods, these rapid fluctuations will be treated in the analysis as random error around an average trajectory. In reality, they could reflect an additional pattern of injecting frequency and possibly the degree of variability could be an additional dimension describing the typology of behavior. Further analyses, also informed by qualitative research in IDU should assess the existence of such patterns.

Our analysis was also restricted in terms of sample size, which was particularly pronounced in the analysis considering incidence of HIV and HCV. Further limitation of sample size resulted from missing information for some of the variables from a substantial fraction of the participants.

5. Conclusions

We demonstrated the existence of distinct longitudinal patterns of changes in drug use in the ACS that correlate with the risk of acquiring HIV infection. The majority of IDUs in the cohort had stable risk behavior, but there were also groups in which injecting decreased over time. The patterns were similar to those observed in previous studies among IDUs in the USA, which suggest some universality of such patterns despite cultural differences. Group membership was associated with duration of injecting before cohort entry and time of cohort entry. While the analysis presented here was limited to one risk factor, namely frequency of injecting, future analyses can jointly include several risk factors. This opens up the possibility of identifying risk profiles, linking them to demographic and socio-economic determinants, and analyzing their impact on the risk of acquiring infection. Intervention efforts can then be targeted to specific risk profiles, and timing and intervention aims can be improved. Also, targeted research may be conducted to gain insight into why individuals in some groups change their risk behavior whereas those in other groups continue the same level of risk taking for many years.

References

Aceijas, C., Rhodes, T., 2007. Global estimates of prevalence of HCV infection among injecting drug users. Int J Drug Policy 18, 352-358.

Arrandale, V., Koehoorn, M., MacNab, Y., Kennedy, S.M., 2006. How to use SAS® Proc Traj and SAS® Proc Glimmix in Respiratory Epidemiology.

Broidy, L.M., Nagin, D.S., Tremblay, R.E., Bates, J.E., Brame, B., Dodge, K.A., Fergusson, D., Horwood, J.L., Loeber, R., Laird, R., Lynam, D.R., Moffitt, T.E., Pettit, G.S., Vitaro, F., 2003. Developmental trajectories of childhood disruptive behaviors and adolescent delinquency: a six-site, cross-national study. Dev. Psychol. 39, 222-245.

Brook, D.W., Brook, J.S., Zhang, C., Whiteman, M., Cohen, P., Finch, S.J., 2008. Developmental trajectories of cigarette smoking from adolescence to the early thirties: personality and behavioral risk factors. Nicotine Tob Res 10, 1283-1291.

Brook, J.S., Balka, E.B., Ning, Y., Brook, D.W., 2007. Trajectories of cigarette smoking among African Americans and Puerto Ricans from adolescence to young adulthood: associations with dependence on alcohol and illegal drugs. Am. J. Addict. 16, 195-201.

Cjte, S., Tremblay, R.E., Nagin, D., Zoccolillo, M., Vitaro, F., 2002. The development of impulsivity, fearfulness, and helpfulness during childhood: patterns of consistency and change in the trajectories of boys and girls. J. Child Psychol. Psychiatry 43, 609-618.

Fennema, J.S., Van Ameijden, E.J., Van Den Hoek, A., Coutinho, R.A., 1997. Young and recent-onset injecting drug users are at higher risk for HIV. Addiction 92, 1457-1465.

Genberg, B.L., Gange, S.J., Go, V.F., Celentano, D.D., Kirk, G.D., Mehta, S.H., 2011. Trajectories of injection drug use over 20 years (1988-2008) in Baltimore, Maryland. Am. J. Epidemiol. 173, 829-836.

Haviland, A., Nagin, D.S., Rosenbaum, P.R., 2007. Combining propensity score matching and group-based trajectory analysis in an observational study. Psychol. Methods 12, 247-267.

Hser, Y.I., Hamilton, A., Niv, N., 2009. Understanding Drug Use Over the Life Course: Past, Present, and Future. J Drug Issues 31, 231-236.

Hser, Y.I., Huang, D., Chou, C.P., Anglin, M.D., 2007. Trajectories of heroin addiction: growth mixture modeling results based on a 33-year follow-up study. Eval. Rev. 31, 548-563.

Hu, M.C., Muthen, B., Schaffran, C., Griesler, P.C., Kandel, D.B., 2008. Developmental trajectories of criteria of nicotine dependence in adolescence. Drug Alcohol Depend. 98, 94-104.

Huang, D.Y., Evans, E., Hara, M., Weiss, R.E., Hser, Y.I., 2011. Employment Trajectories: Exploring Gender Differences and Impacts of Drug Use. J. Vocat. Behav. 79, 277-289.

Ingvar Rosendahl, K., Rosaria Galanti, M., Gilljam, H., 2008. Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: differences and implications. Nicotine Tob Res 10, 1021-1027.

Jackson, K.M., Sher, K.J., 2008. Comparison of longitudinal phenotypes based on alternate heavy drinking cut scores: a systematic comparison of trajectory approaches III. Psychol. Addict. Behav. 22, 198-209.

Jackson, K.M., Sher, K.J., Schulenberg, J.E., 2008. Conjoint developmental trajectories of young adult substance use. Alcohol. Clin. Exp. Res. 32, 723-737.

Jones, B.S., Nagin, D.S., Roeder, K., 2001. A SAS Procedure Based on Mixture Models. Sociological Methods & Research 29, 374-393.

Jung, T., Wickrama, K.A., 2008. An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. Soc. Personal. Psychol. Compass 2, 302-317.
Lacourse, E., Cote, S., Nagin, D.S., Vitaro, F., Brendgen, M., Tremblay, R.E., 2002. A longitudinal-experimental approach to testing theories of antisocial behavior development. Dev. Psychopathol. 14, 909-924.
Lacourse, E., Nagin, D., Tremblay, R.E., Vitaro, F., Claes, M., 2003. Developmental trajectories of boys' delinquent group membership and facilitation of violent behaviors during adolescence. Dev. Psychopathol. 15, 183-197.
Langendam, M.W., van Haastrecht, H.J., van Ameijden, E.J., 1999. The validity of drug users' self-reports in a non-treatment setting: prevalence and predictors of incorrect reporting methadone treatment modalities. Int. J. Epidemiol. 28, 514-520.
Lessov-Schlaggar, C.N., Hops, H., Brigham, J., Hudmon, K.S., Andrews, J.A., Tildesley, E., McBride, D., Jack, L.M., Javitz, H.S., Swan, G.E., 2008. Adolescent smoking trajectories and nicotine dependence. Nicotine Tob Res 10, 341-351.
Littell, R.C., 1996. SAS system for mixed models. Cary, NC: SAS Inst.
March, J.C., Oviedo-Joekes, E., Romero, M., 2007. Factors associated with reported hepatitis C and HIV among injecting drug users in ten European cities. Enferm. Infecc. Microbiol. Clin. 25, 91-97.
Martino, S.C., Ellickson, P.L., McCaffrey, D.F., 2008. Developmental trajectories of substance use from early to late adolescence: a comparison of rural and urban youth. J Stud Alcohol Drugs 69, 430-440.
Nagin, D.S., 1999. Analyzing Developmental Trajectories: A Semiparametric, Group-Based Approach. Psychol. Methods 4, 139-157.
Nagin, D.S., Odgers, C.L., 2010. Group-based trajectory modeling in clinical research. Annu. Rev. Clin. Psychol. 6, 109-138.
Oh, W., Rubin, K.H., Bowker, J.C., Booth-LaForce, C., Rose-Krasnor, L., Laursen, B., 2008. Trajectories of social withdrawal from middle childhood to early adolescence. J. Abnorm. Child Psychol. 36, 553-566.
Orlando, M., Tucker, J.S., Ellickson, P.L., Klein, D.J., 2005. Concurrent use of alcohol and cigarettes from adolescence to young adulthood: an examination of developmental trajectories and outcomes. Subst. Use Misuse 40, 1051-1069.
Prendergast, M., Huang, D., Evans, E., Hser, Y.I., 2010. Are There Gender Differences in Arrest Trajectories among Adult Drug Abuse Treatment Participants? J Drug Issues 40, 7-26.
Proust-Lima, C., Sene, M., Taylor, J.M., Jacqmin-Gadda, H., 2014. Joint latent class models for longitudinal and time-to-event data: a review. Stat. Methods Med. Res. 23, 74-90.
Schulenberg, J., O'Malley, P.M., Bachman, J.G., Wadsworth, K.N., Johnston, L.D., 1996. Getting drunk and growing up: trajectories of frequent binge drinking during the transition to young adulthood. J. Stud. Alcohol 57, 289-304.
Termorshuizen, F., Krol, A., Prins, M., van Ameijden, E.J., 2005. Long-term outcome of chronic drug use: the Amsterdam Cohort Study among Drug Users. Am. J. Epidemiol. 161, 271-279.
Tremblay, R.E., Nagin, D.S., Seguin, J.R., Zoccolillo, M., Zelazo, P.D., Boivin, M., Perusse, D., Japel, C., 2005. Physical aggression during early childhood: trajectories and predictors. Can Child Adolesc Psychiatr Rev 14, 3-9.
van Ameijden, E.J., Coutinho, R.A., 2001. Large decline in injecting drug use in Amsterdam, 1986-1998: explanatory mechanisms and determinants of injecting transitions. J. Epidemiol. Community Health 55, 356-363.

van den Hoek, J.A., Coutinho, R.A., van Haastrecht, H.J., van Zadelhoff, A.W., Goudsmit, J., 1988. Prevalence and risk factors of HIV infections among drug users and drug-using prostitutes in Amsterdam. AIDS 2, 55-60.
van den Hoek, J.A., van Haastrecht, H.J., Goudsmit, J., de Wolf, F., Coutinho, R.A., 1990. Prevalence, incidence, and risk factors of hepatitis C virus infection among drug users in Amsterdam. J. Infect. Dis. 162, 823-826.
Wanner, B., Vitaro, F., Ladouceur, R., Brendgen, M., Tremblay, R.E., 2006. Joint trajectories of gambling, alcohol and marijuana use during adolescence: a person- and variable-centered developmental approach. Addict. Behav. 31, 566-580.
Weber, R., Huber, M., Rickenbach, M., Furrer, H., Elzi, L., Hirschel, B., Cavassini, M., Bernasconi, E., Schmid, P., Ledergerber, B., 2009. Uptake of and virological response to antiretroviral therapy among HIV-infected former and current injecting drug users and persons in an opiate substitution treatment programme: the Swiss HIV Cohort Study. HIV Med. 10, 407-416.
Xie, H., Drake, R., McHugo, G., 2006. Are there distinctive trajectory groups in substance abuse remission over 10 years? An application of the group-based modeling approach. Adm. Policy Ment. Health 33, 423-432.

Figure legends

Figure 1 a-d). Trajectories describing changes in the frequency of injecting drugs (a and b) and probability of having injected drugs since last visit (c and d) over the time in the cohort

Footnote: Figures a) and c) provide the average tendency per group (median values based on logarithmic transformation), horizontal lines indicate thresholds between categories of the original variable (Figure a) or dichotomized response regarding injecting since the last visit (Figure c). For example, the average behavior in group 3 in Figure c) is having injected since last visit in the years 0 to 2.5, but after 2.5 years is not having injected since last visit. Correspondingly, average behavior in group 3in a) is injecting 2-6 times per week in the years 0 to 5, and drops to <1 per month during years 5 to 10.

Figures b) and d) present the full frequency distributions within each latent group over the time of the study. For each time interval of one year individual responses are inversely weighted by the number of responses for the individual and all individuals who provided responses within the time interval are considered 100%. For example, in Figure d) in group 4 in the beginning of follow-up nearly everybody was injecting drugs but after 10 years nearly nobody was injecting drugs.

Tables

Table 1. Time variables associated with ≥daily versus <daily injecting among injecting drug users in the Amsterdam Cohort Study among Drug Users *

Variable	Odds ratio (95% Confidence interval)	
	Crude	Adjusted**
Duration of injecting at cohort entry (per five years)	1.11 (0.99-1.24)	1.22 (1.06-1.41)
Year of cohort entry (per five years change)	0.64 (0.53-0.78)	0.55 (0.43-0.69)
Time in the cohort (per five years)	0.25 (0.20-0.32)	0.24 (0.19-0.31)

* Random effects logistic regression model restricted to participants for whom information in the time window of 4.5-5.5 years in the cohort was available (N=542); each subject had two outcomes: injecting at cohort entry and five years later, outcomes of the same subject were linked by the subject ID

** adjusted for all variables in the table, sex and age at cohort entry, preferred drug of use, and ever sharing syringes

Table 2. BIC and adjusted BIC values for the growth mixture models with an increasing number of latent classes

	BIC		Adjusted BIC	
Number of classes	Ordinal model*	Binary model**	Ordinal model*	Binary model**
2	37483.38	12232.2	37462.69	12219.79
3	35819.25	11251.14	35791.67	11231.83
4	35151.95	10940.95	35117.47	10914.75
5	34700.5	10706.63	34659.13	10673.53
6	34500.1	10612.32	34451.83	10572.33
7	34277.1	10522.09	34221.94	10475.20

* ordinal model uses the frequency of injecting on the original scale

** binary model uses information whether person injected drugs in the period since last visit

Table 3. Cross-tabulation of patterns with regard to frequency of injecting and probability of injecting (numbers are row percent)

	Late decrease	*High probability of injecting*	*Early decrease*	*Stopping and starting*	*Low probability of injecting*
Constant daily or several times daily injecting	2.7%	97.3%	0.0%	0.0%	0.0%
Decrease in injecting	44.9%	5.6%	47.2%	2.2%	0.0%
Every 2nd day and less frequent injecting	17.6%	71.2%	1.7%	9.4%	0.0%
Rare to no injecting	0.0%	0.0%	7.1%	1.8%	91.1%
Variable injecting	5.1%	4.4%	27.0%	62.0%	1.5%

Table 4. Characteristics associated with different trajectories of injecting frequency over time (multinomial logistic regression, the reference group is constant daily and more than daily injecting)

	Decrease in injecting		*Every 2nd day and less frequent injecting*		*Rare to no injecting*		*Variable injecting*	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Male vs. female	0.73	0.39, 1.36	1.05	0.63, 1.75	0.81	0.43, 1.51	1.14	0.63, 2.06
HIV status at entry (positive vs. negative)	0.82	0.43, 1.56	1.00	0.6, 1.65	0.81	0.41, 1.60	0.80	0.43, 1.47
Ever sharing syringes at entry (no vs. yes)	0.80	0.31, 2.07	0.67	0.29, 1.56	0.88	0.35, 2.26	0.55	0.22, 1.36
… (unknown vs. yes)	0.41	0.17, 0.99	0.69	0.34, 1.43	1.15	0.49, 2.68	0.60	0.27, 1.33
Drug of choice in the last six months at entry (no injection vs. cocaine and heroin)	1.07	0.29, 3.97	2.05	0.74, 5.74	58.56	20.43, 167.92	10.07	3.60, 28.20
…(heroin vs. cocaine and heroin)	0.49	0.2, 1.21	0.70	0.36, 1.36	2.05	0.86, 4.86	0.90	0.40, 2.00
… (cocaine vs. cocaine and heroin)	0.92	0.36, 2.34	0.78	0.36, 1.72	1.02	0.34, 3.03	1.07	0.43, 2.64
… (amphetamine vs. cocaine and heroin)	1.25	0.36, 4.27	1.09	0.38, 3.11	1.20	0.26, 5.65	2.08	0.66, 6.53
… (methadone vs. cocaine and heroin)	0.51	0.14, 1.89	0.18	0.05, 0.68	0.10	0.01, 1.03	0.22	0.05, 0.91
… (unknown vs. cocaine and heroin)	0.20	0.02, 1.7	0.63	0.24, 1.68	1.16	0.22, 6.26	0.47	0.09, 2.42
Age at cohort entry [per year]	1.00	0.95, 1.06	1.06	1.00, 1.11	0.96	0.91, 1.02	1.03	0.98, 1.09
Duration of injecting at cohort entry [per year]	0.93	0.89, 0.98	0.99	0.95, 1.03	0.91	0.86, 0.95	0.96	0.91, 1.01
Year of cohort entry [per year]	0.94	0.84, 1.06	0.91	0.82, 1.00	0.77	0.70, 0.85	0.82	0.74, 0.90

OR- odds ratio, CI- confidence interval

Table 5. Patterns of change in injecting frequency and corresponding cumulative incidence of HIV and HCV over 10 years (estimates from Kaplan-Meier analysis)

Pattern of injecting	HIV seronegative at cohort entry [n]	HIV free survival after 10 years [95% CI]*	HCV seronegative at cohort entry [n]	HCV free survival after 10 years [95% CI]**
Rare to no injecting	140	0.97 [0.91, 0.99]	34	0.65 [0.43, 0.80]
Every 2nd day and less frequent	159	0.71 [0.62-0.78]	36	0.59 [0.39-0.75]
Constant daily or more than daily injecting	73	0.79 [0.66, 0.87]	15	0.62 [0.28, 0.84]
Decrease in injecting	65	0.87 [0.74, 0.93]	16	0.52 [0.23, 0.75]
Variable injecting	107	0.84 [0.74, 0.90]	22	0.66 [0.36, 0.84]

* log-rank test for difference across groups $p<0.0001$

** log-rank test for difference across groups $p=0.76$